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=> d his

     (FILE 'HCAPLUS' ENTERED AT 10:17:02 ON 22 FEB 2001)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 10:19:52 ON 22 FEB 2001
                 E NITRIC OXIDE/CN
L1             1 S E3
                 E NITRIC OXIDE SYTHETASE/CN
                 E NITRIC OXIDE SYNTHASE
                 E NITRIC OXIDE SYNTHASE/CN
L2             1 S E3

     FILE 'HCAPLUS' ENTERED AT 10:20:53 ON 22 FEB 2001
L3          4191 S IL 12 OR INTERLEUKIN 12
L4         11519 S ADJUVANT#
L5        125212 S L1  OR L2 OR (NO OR NITRIC OXIDE)
L6           142 S L3 (L) L4
L7          9442 S IMMUNOSTIM?
L8            84 S L6 AND L7
L9             2 S L8 AND L5
L10            4 S L6 AND L5
L11            7 S L3 AND L4 AND L5

     FILE 'REGISTRY' ENTERED AT 10:22:54 ON 22 FEB 2001
L12            2 S 50903-99-6 OR 17035-90-4

     FILE 'HCAPLUS' ENTERED AT 10:23:18 ON 22 FEB 2001
L13         1678 S L12
L14          875 S L NAME OR L NMMA
L15         1774 S L13 OR L14
L16            0 S L6 AND L15
L17            2 S L3 AND L14
L18        25593 S VACCINE#
L19          441 S L3 AND L18
L20           12 S L19 AND L5
L21            1 S L19 AND L14
L22           15 S L9 OR L10 OR L11 OR L17 OR L21 OR L20
L23         3172 S IMMUN? (3A) STIMUL?
L24           58 S L3 AND L23
L25            3 S L24 AND (L14 OR L5)
L26           16 S L25 OR L22

     FILE 'USPATFULL' ENTERED AT 10:28:48 ON 22 FEB 2001
L27         1535 S L1 OR L2
L28           65 S L12
L29         1550 S L27 OR L28
L30         4119 S NITRIC OXIDE OR L NAME OR L NMMA
L31          705 S (INTERLEUKIN 12 OR IL12 OR IL 12)
L32          130 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM
L33            9 S L32 AND L30
L34          136 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM,TI,AB
L35            9 S L34 AND (L29 OR L30)
L36            9 S L33 OR L35

     FILE 'USPATFULL, HCAPLUS' ENTERED AT 10:32:18 ON 22 FEB 2001
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L37 25 DUP REM L36 L26 (0 DUPLICATES REMOVED)

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=> fil reg

FILE 'REGISTRY' ENTERED AT 10:33:07 ON 22 FEB 2001
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STRUCTURE FILE UPDATES:   20 FEB 2001  HIGHEST RN 322637-11-6
DICTIONARY FILE UPDATES:  20 FEB 2001  HIGHEST RN 322637-11-6

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> d que l1;d l1

L1             1 SEA FILE=REGISTRY ABB=ON  "NITRIC OXIDE"/CN



L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2001 ACS
RN   10102-43-9  REGISTRY
CN   Nitrogen oxide (NO) (8CI, 9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Amidogen, oxo-
CN   Nitric oxide
CN   Nitric oxide (NO)
CN   Nitric oxide trimer
CN   Nitrogen monooxide
CN   Nitrogen monoxide
CN   Nitrogen oxide (N4O4)
CN   Nitrogen(II) oxide
CN   Nitrosyl radical
DR   53851-19-7, 51005-20-0, 51005-21-1, 90452-29-2
MF   N O
CI   COM
LC   STN Files:   AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT,
       APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS,
       CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN,
       CSCHEM, CSNB, DDFU, DETHERM*, DIPPR*, DRUGU, DRUGUPDATES, EMBASE,
       GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS,
       NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT,
       TRCTHERMO*, TULSA, ULIDAT, USPATFULL, VETU, VTB
         (*File contains numerically searchable property data)
     Other Sources:   DSL**, EINECS**, TSCA**
         (**Enter CHEMLIST File for up-to-date regulatory information)


N==O
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56543 REFERENCES IN FILE CA (1967 TO DATE)
368 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
56698 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> d que l2;d l2

L2 1 SEA FILE=REGISTRY ABB=ON "NITRIC OXIDE SYNTHASE"/CN

L2 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2001 ACS
RN 125978-95-2 REGISTRY
CN Synthase, nitric oxide (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Endothelium-derived relaxation factor-forming enzyme
CN Endothelium-derived relaxing factor synthase
CN **Nitric oxide synthase**
CN Nitric oxide synthetase
CN NO synthase
MF Unspecified
CI MAN
SR CA
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CHEMCATS, CIN, CSCHEM, EMBASE, IPA, PROMT, TOXLINE, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
12089 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
12149 REFERENCES IN FILE CAPLUS (1967 TO DATE)

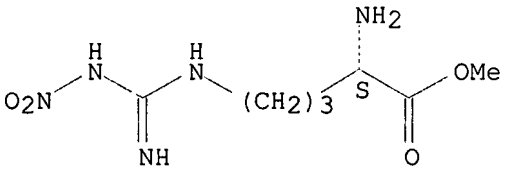
=> d que l12;d l12 1-2

L12 2 SEA FILE=REGISTRY ABB=ON 50903-99-6 OR 17035-90-4

L12 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2001 ACS
RN **50903-99-6** REGISTRY
CN L-Ornithine, N5-[imino(nitroamino)methyl]-, methyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN L-NAME
CN L-NAME
CN N-Nitro-L-arginine methyl ester
CN N.omega.-Nitro-L-arginine methyl ester
CN N.omega.-Nitro-L-arginine methyl ester
CN NAME
CN NG-Nitro-L-arginine Me ester
CN NG-Nitro-L-arginine methyl ester
FS STEREOSEARCH
DR 162715-84-6, 126265-24-5, 189639-12-1
MF C7 H15 N5 O4
CI COM

LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS, CIN, DIOGENES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

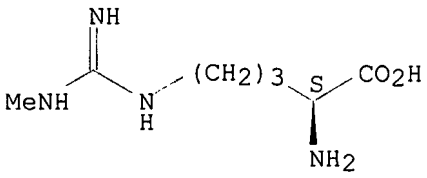
Absolute stereochemistry.



1086 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1089 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L12 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2001 ACS
RN **17035-90-4** REGISTRY
CN L-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ornithine, N5-(methylamidino)-, L- (8CI)
OTHER NAMES:
CN .omega.-N-Methylarginine
CN .omega.-N-Monomethylarginine
CN L-NG-Methylarginine
CN L-NMA
CN L-NMMA
CN Methylarginine
CN N5-(Methylamidino)-L-ornithine
CN NG-Methyl-L-arginine
CN NG-Methylarginine
CN NG-Monomethyl-L-arginine
CN NG-Monomethylarginine
CN Targinine
FS STEREOSEARCH
DR 42342-68-7
MF C7 H16 N4 O2
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN,
CSCHEM, DDFU, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.



718 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
718 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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     (FILE 'HCAPLUS' ENTERED AT 10:17:02 ON 22 FEB 2001)
               DEL HIS Y

     FILE 'REGISTRY' ENTERED AT 10:19:52 ON 22 FEB 2001
               E NITRIC OXIDE/CN
L1           1 S E3
               E NITRIC OXIDE SYTHETASE/CN
               E NITRIC OXIDE SYNTHASE
               E NITRIC OXIDE SYNTHASE/CN
L2           1 S E3

     FILE 'HCAPLUS' ENTERED AT 10:20:53 ON 22 FEB 2001
L3        4191 S IL 12 OR INTERLEUKIN 12
L4       11519 S ADJUVANT#
L5      125212 S L1  OR L2 OR (NO OR NITRIC OXIDE)
L6         142 S L3 (L) L4
L7        9442 S IMMUNOSTIM?
L8          84 S L6 AND L7
L9           2 S L8 AND L5
L10          4 S L6 AND L5
L11          7 S L3 AND L4 AND L5

     FILE 'REGISTRY' ENTERED AT 10:22:54 ON 22 FEB 2001
L12          2 S 50903-99-6 OR 17035-90-4

     FILE 'HCAPLUS' ENTERED AT 10:23:18 ON 22 FEB 2001
L13       1678 S L12
L14        875 S L NAME OR L NMMA
L15       1774 S L13 OR L14
L16          0 S L6 AND L15
L17          2 S L3 AND L14
L18      25593 S VACCINE#
L19        441 S L3 AND L18
L20         12 S L19 AND L5
L21          1 S L19 AND L14
L22         15 S L9 OR L10 OR L11 OR L17 OR L21 OR L20
L23       3172 S IMMUN? (3A) STIMUL?
L24         58 S L3 AND L23
L25          3 S L24 AND (L14 OR L5)
L26         16 S L25 OR L22

     FILE 'USPATFULL' ENTERED AT 10:28:48 ON 22 FEB 2001
L27       1535 S L1 OR L2
L28         65 S L12
L29       1550 S L27 OR L28
L30       4119 S NITRIC OXIDE OR L NAME OR L NMMA
L31        705 S (INTERLEUKIN 12 OR IL12 OR IL 12)
L32        130 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM
L33          9 S L32 AND L30
L34        136 S (INTERLEUKIN 12 OR IL12 OR IL 12)/CLM,TI,AB
L35          9 S L34 AND (L29 OR L30)
L36          9 S L33 OR L35
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FILE 'USPATFULL, HCAPLUS' ENTERED AT 10:32:18 ON 22 FEB 2001
L37 25 DUP REM L36 L26 (0 DUPLICATES REMOVED)

FILE 'REGISTRY' ENTERED AT 10:33:07 ON 22 FEB 2001

=> fil uspatfull hcaplus

FILE 'USPATFULL' ENTERED AT 10:33:46 ON 22 FEB 2001
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=> d bib ab it 1-25

L37 ANSWER 1 OF 25 USPATFULL
AN 2000:70440 USPATFULL
TI Enhanced activation of natural killer cells using an NK cell activator and a hydrogen peroxide scavenger or inhibitor
IN Hellstrand, Jan Urban Kristoffer, Gothenburg, Sweden
Hermodsson, Svante Hermod, Molndal, Sweden
PA Maxim Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6071509 20000606
AI US 1996-681108 19960722 (8)
RLI Continuation of Ser. No. US 1994-287200, filed on 8 Aug 1994, now abandoned
DT Utility
EXNAM Primary Examiner: Celsa, Bennett; Assistant Examiner: Garcia, Maurie
LREP Knobbe, Martens, Olson & Bear, LLP
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 1174
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An improved method for the prevention of the inactivation of natural killer (NK) cells and the enhanced activation of NK cells in the presence of monocytes using a combination of a natural killer cell activator and a compound effective to inhibit the production or release of intracellular hydrogen peroxide, or a hydrogen peroxide scavenger, is disclosed. The method is useful, for example, in the treatment of solid tumors, metastases and viral infection.
IT Monocyte
(histamine augmentation of natural killer cell cytotoxicity against tumor cells in presence of)
IT Neoplasm inhibitors
(interleukin-2 and histamine or H2-receptor agonist as)
IT Pharmaceutical dosage forms
(of interleukin-2 and histamine or H2-receptor agonist, for tumor growth and metastasis inhibition)
IT Neurotransmitter agonists
(histaminic H2, interleukin-2 and tumor growth and metastasis inhibition with)

IT Lymphokines and Cytokines
(interleukin 2, histamine or H2-receptor agonist and, tumor growth and metastasis inhibition with)
IT Neoplasm inhibitors
(metastasis, interleukin-2 and histamine or H2-receptor agonist as)
IT Lung, neoplasm
(metastasis, prevention of, with histamine and interleukin-2)
IT Lymphocyte
(natural killer, cytotoxicity of, against tumor cells, histamine and/or interleukin-2 effect on)
IT 51-45-6, Histamine, biological studies 51-45-6D, Histamine, analogs
(interleukin-2 and, tumor growth and metastasis inhibition with)
IT 65119-89-3, Dimaprit
(lung metastasis inhibition with)
IT 136218-98-9
(tumor growth and metastasis inhibition with)

L37 ANSWER 2 OF 25 USPATFULL
AN 2000:61190 USPATFULL
TI Enhanced activation of NK cells using an NK cell activator and a hydrogen peroxide scavenger or inhibitor
IN Hellstrand, Jan Urban Kristoffer, Goteborg, Sweden
Hermodsson, Svante Hermod, Molndal, Sweden
PA Maxim Pharmaceuticals, Inc., San Diego, CA, United States (U.S. corporation)
PI US 6063373 20000516
AI US 1997-932406 19970917 (8)
RLI Continuation of Ser. No. US 1996-602514, filed on 20 Feb 1996, now abandoned which is a division of Ser. No. US 1994-287200, filed on 8 Aug 1994, now abandoned which is a continuation-in-part of Ser. No. US 1992-843052, filed on 2 Mar 1992, now patented, Pat. No. US 5348739 which is a continuation-in-part of Ser. No. US 1989-409357, filed on 19 Sep 1989, now abandoned
DT Utility
EXNAM Primary Examiner: Celsa, Bennett; Assistant Examiner: Garcia, Maurie
LREP Knobbe, Martens, Olson & Bear, LLP
CLMN Number of Claims: 5
ECL Exemplary Claim: 1
DRWN 7 Drawing Figure(s); 10 Drawing Page(s)
LN.CNT 1097
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An improved method for the prevention of the inactivation of natural killer (NK) cells and the enhanced activation of NK cells in the presence of monocytes using a combination of a natural killer cell activator and a compound effective to inhibit the production or release of intracellular hydrogen peroxide, or a hydrogen peroxide scavenger, is disclosed. The method is useful, for example, in the treatment of solid tumors, metastases and viral infection.
IT Monocyte
(histamine augmentation of natural killer cell cytotoxicity against tumor cells in presence of)
IT Neoplasm inhibitors
(interleukin-2 and histamine or H2-receptor agonist as)
IT Pharmaceutical dosage forms

(of interleukin-2 and histamine or H2-receptor agonist, for tumor growth and metastasis inhibition)
IT Neurotransmitter agonists
(histaminic H2, interleukin-2 and tumor growth and metastasis inhibition with)
IT Lymphokines and Cytokines
(interleukin 2, histamine or H2-receptor agonist and, tumor growth and metastasis inhibition with)
IT Neoplasm inhibitors
(metastasis, interleukin-2 and histamine or H2-receptor agonist as)
IT Lung, neoplasm
(metastasis, prevention of, with histamine and interleukin-2)
IT Lymphocyte
(natural killer, cytotoxicity of, against tumor cells, histamine and/or interleukin-2 effect on)
IT 51-45-6, Histamine, biological studies 51-45-6D, Histamine, analogs
(interleukin-2 and, tumor growth and metastasis inhibition with)
IT 65119-89-3, Dimaprit
(lung metastasis inhibition with)
IT 136218-98-9
(tumor growth and metastasis inhibition with)

L37 ANSWER 3 OF 25 USPATFULL
AN 2000:27800 USPATFULL
TI Recombinant swinepox virus
IN Cochran, Mark D., Carlsbad, CA, United States
Junker, David E., San Diego, CA, United States
PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)
PI US 6033904 20000307
AI US 1995-480640 19950607 (8)
RLI Continuation-in-part of Ser. No. US 1995-375922, filed on 19 Jan 1995 which is a continuation-in-part of Ser. No. WO 1994-US8277, filed on 22 Jul 1994 which is a continuation-in-part of Ser. No. US 1993-97554, filed on 22 Jul 1993, now patented, Pat. No. US 5869312 And a continuation-in-part of Ser. No. US 1992-820154, filed on 13 Jan 1992, now patented, Pat. No. US 5382425, issued on 17 Jan 1995
DT Utility
EXNAM Primary Examiner: Mosher, Mary E.; Assistant Examiner: Salini, Ali R
LREP White, John P.Copper & Dunham LLP
CLMN Number of Claims: 32
ECL Exemplary Claim: 1,7
DRWN 114 Drawing Figure(s); 114 Drawing Page(s)
LN.CNT 8999
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a recombinant swinepox virus comprising a foreign DNA sequence inserted into the swinepox virus genomic DNA, wherein the foreign DNA sequence is inserted within a HindIII N fragment of the swinepox virus genomic DNA and is capable of being expressed in a swinepox virus infected host cell. The invention further provides homology vectors, vaccines and methods of immunization.
IT Glycoproteins, specific or class
(A, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class

(B, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(C, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(E, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(E1, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(E2, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(F, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(G, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Gene, microbial
(I4L, foreign DNA insertion into; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Gene, microbial
(I7L, foreign DNA insertion into; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(M (matrix), viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(N (nucleocapsid), viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(NP (nucleoprotein), viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(ORF 7, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(VP2, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(VP3, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Lipoproteins
(VP4, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Avian infectious bronchitis virus
IT Bovine diarrhea virus
IT Bovine herpesvirus 1
IT Bovine parainfluenza virus 3
IT Bovine respiratory syncytial virus
IT Chicken anemia virus
IT Equid herpesvirus 1
IT Equine influenza virus
IT Feline immunodeficiency virus
IT Gallid herpesvirus

IT Gallid herpesvirus 1
IT Hepatitis B virus
IT Hepatitis C virus
IT Hog cholera virus
IT Human herpesvirus
IT Human herpesvirus 1
IT Human herpesvirus 2
IT Human herpesvirus 3
IT Human herpesvirus 4
IT Human herpesvirus 5
IT Human herpesvirus 6
IT Human herpesvirus 7
IT Human immunodeficiency virus
IT Infectious bursal disease virus
IT Influenza virus
IT Measles virus
IT Newcastle disease virus
IT Pseudorabies virus
IT Pseudorabies virus 3
IT Rabies virus
IT Swine infertility and respiratory syndrome virus
IT Swine influenza virus
(antigens from; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Proteins, specific or class
(attachment, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gD, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gE, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gH, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gI, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gp48, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gp50, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(gp53, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Antigens
(hepatitis B core; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Antigens
(hepatitis B surface; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Plasmid vectors
(homol. vectors; recombinant swinepox virus for expression of foreign

antigens in vaccine prepns.)
IT Hemopoietins
(myelomonocytic growth factors, chicken; recombinant swinepox virus for
expression of foreign antigens in vaccine prepns.)
IT Swinepox virus
IT Virus vectors
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Promoter (genetic element)
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Antigens
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Cytokines
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Hemagglutinins
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Interferons
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Interleukin 12
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Interleukin 2
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Interleukin 6
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Interleukin receptors
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Glycoproteins, specific or class
(spike, viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Vaccines
(synthetic; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT Envelope proteins
IT Polyproteins
IT gag proteins
(viral; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT 9001-45-0, .beta.-Glucuronidase 9031-11-2, .beta.-Galactosidase
(Escherichia coli; recombinant swinepox virus for expression of foreign
antigens in vaccine prepns.)
IT 9001-67-6, Neuraminidase 83869-56-1, GM-CSF
(recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)
IT 150549-26-1 150549-27-2 150549-28-3 158969-89-2 222351-61-3
222351-62-4 222351-63-5 222351-64-6 222351-65-7 222652-83-7
222652-84-8 222652-85-9 222652-86-0 222652-87-1 222652-88-2

222652-89-3 222652-90-6 222652-91-7 222652-92-8 222652-93-9
222652-94-0 243925-27-1, 7: PN: US6033904 SEQID: 9 unclaimed DNA
243925-28-2, 8: PN: US6033904 SEQID: 10 unclaimed DNA 243925-29-3, 9:
PN: US6033904 SEQID: 13 unclaimed DNA 243925-30-6 243925-31-7
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243925-42-0 243925-43-1 243925-44-2 243925-45-3 243925-46-4
243925-47-5 243925-48-6 243925-49-7 243925-50-0 243925-51-1
243925-52-2 243925-53-3 243925-54-4 243925-56-6 243925-59-9
243925-62-4 243925-63-5 243925-64-6 243925-65-7 243925-66-8
243925-67-9 243925-68-0 243925-69-1 243925-70-4 243925-71-5
243925-72-6 260238-94-6 260238-95-7 260238-96-8 260238-97-9
260238-98-0 260238-99-1 260239-02-9 260239-03-0 260239-04-1
260239-05-2 260239-06-3 260239-07-4 260239-08-5 260239-09-6
260239-10-9 260239-11-0 260239-12-1 260239-13-2 260239-14-3
260239-15-4 260239-16-5 260239-17-6 260239-18-7 260239-19-8
260239-20-1 260239-21-2 260239-22-3 260239-23-4 260239-24-5
260239-25-6 260239-26-7 260239-27-8 260239-28-9 260239-29-0
260239-30-3 260239-31-4 260239-32-5 260239-33-6 260239-34-7
260239-38-1 260239-40-5 260239-41-6 260239-42-7 260239-43-8
260239-44-9 260239-45-0 260239-46-1 260239-47-2 260239-48-3
260239-49-4 260239-50-7 260239-51-8 260239-52-9 260239-53-0
260239-54-1 260239-55-2 260239-56-3 260239-57-4 260239-58-5
260239-59-6 260239-60-9 260239-61-0
(unclaimed nucleotide sequence; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT 177698-75-8 260238-89-9 260238-90-2 260238-91-3 260238-92-4
260238-93-5 260239-00-7 260239-01-8 260239-35-8 260239-36-9
260239-37-0 260239-39-2 260365-27-3
(unclaimed protein sequence; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

IT 72-18-4, L-Valine, properties 2640-07-5 42155-95-3 260052-07-1
260052-08-2 260052-09-3 260052-10-6 260052-11-7 260052-12-8
260052-13-9 260052-14-0 260052-15-1 260052-16-2 260052-17-3
260052-18-4 260052-19-5 260052-20-8 260052-21-9 260052-22-0
260052-23-1 260052-24-2
(unclaimed sequence; recombinant swinepox virus for expression of foreign antigens in vaccine prepns.)

L37 ANSWER 4 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:240985 HCAPLUS
DN 132:292701
TI Novel methods for therapeutic vaccination
IN Steinaa, Lucilla; Mouritsen, Soren; Nielsen, Klaus Gregorious; Haaning, Jesper; Leach, Dana; Dalum, Iben; Gautam, Anand; Birk, Peter; Karlsson, Gunilla
PA M Amp E Biotech A/s, Den.
SO PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000020027	A2	20000413	WO 1999-DK525	19991005

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PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000020027	A2	20000413	WO 1999-DK525	19991005
WO 2000020027	A3	20001012		

W: AE, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI DK 1998-1261 19981005
US 1998-105011 19981020

AB A method is disclosed for inducing cell-mediated immunity against cellular antigens. More specifically, the invention provides for a method for inducing cytotoxic T-lymphocyte immunity against weak antigens, notably self-proteins. The method entails that antigen presenting cells are induced to present at least one CTL epitope of the weak antigen and at the same time presenting at least one foreign T-helper lymphocyte epitope. In a preferred embodiment, the antigen is a cancer specific antigen, e.g. prostate specific membrane antigen (PSM), Her2, or FGF8b. The method can be exercised by using traditional polypeptide vaccination, but also by using live attenuated vaccines or nucleic acid vaccination. The invention furthermore provides immunogenic analogs of PSM, Her2 and FGF8b, as well as nucleic acid mols. encoding these analogs. Also vectors and transformed cells are disclosed. The invention also provides for a method for identification of immunogenic analogs of weak or non-immunogenic antigens.

IC A61K039-00
CC 15-2 (Immunochemistry)
Section cross-reference(s): 3, 63
ST weak antigen **vaccine** cytotoxic T lymphocyte; tumor antigen T cell epitope **vaccine**
IT Antigens

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(17-1A; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AM-1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(APC; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(APRIL; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BAGE; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Chemokines
(C-X-C, Ena78; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT CD antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CD33; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Glycoproteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CD40-L (antigen CD40 ligand); weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CD52; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CDC27; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CO17-1A; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(CS (circumsporozoite), epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DCC (deleted in colorectal cancer); weak antigens inserted with

foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DcR3; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E6; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transcription factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(E7; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Hematopoietin receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(FLT3 receptors; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Glycoproteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GP1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(H-ras; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMTV; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Heat-shock proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HSP 70; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Heat-shock proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HSP 90; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Immunoglobulin receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(IgE type II; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(K-ras; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Lipoprotein receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(LDL, fusion with FUT or fucosyltransferase; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MCP (membrane cofactor protein); weak antigens inserted with foreign T

cell epitope as **vaccines**)

IT Multidrug resistance proteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MDR1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class I; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Histocompatibility antigens
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility complex), class II; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Diglycerides
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-acyl; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(N-ras; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Glycoproteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(P170; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Phosphoproteins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(P210bcr-c-abl; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Prostate-specific antigen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PSA and PSM; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Hemopoietins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Progenipoietin; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transcription factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Rb; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SART-1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Gene, animal
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(SSX; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transcription factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(STAT3; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Mucins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(STn antigen; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TAG-72 (tumor-assocd. glycoprotein 72); weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TPA (tissue protein antigen); weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TRP-1 (tyrosinase-related protein 1); weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TRP-2 (tyrosinase-related protein 2); weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**adjuvant**; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Immunostimulants
(**adjuvants**, Freund's incomplete; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Immunostimulants
(**adjuvants**, Freund's; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Immunostimulants
(**adjuvants**, ISCOMs; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Immunostimulants
(**adjuvants**, Ribi; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Immunostimulants
(**adjuvants**; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(anal; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Animal virus
Bacteria (Eubacteria)
Parasite
(antigen; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bcl-2; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(buccal; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Transcription factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(c-myc; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Diagnosis
(cancer; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT T cell (lymphocyte)
(cytotoxic, epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Mutation
(deletion; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Neoplasm
(diagnosis; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Toxoids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diphtheria, epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Glycophosphoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endoplasmins; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Toxins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enterotoxins, heat-labile; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(epidural; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Mucins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(episialins; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT B cell (lymphocyte)
T cell (lymphocyte)
(epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Hemagglutinins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Functional groups
(farnesyl; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(folate; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Immunoglobulins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fragments; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Vascular endothelial growth factor receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(gene KDR; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Functional groups
(geranyl-geranyl; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Protein motifs
(glycosylation site; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Glycoproteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gp100; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Glycoproteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gp15; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Sialoglycoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gp75; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT T cell (lymphocyte)
(helper cell, epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Phosphoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hsc 70 (heat-shock cognate, 70,000-mol.-wt.); weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(injections, s.c.; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Mutation
(insertion; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Interleukin receptors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(interleukin 13 receptors; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(intracranial; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(intracutaneous; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(intradermal; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Hemolysins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(listeriolysins; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mammaglobin; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melanoma-assocd., MAGE; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melanoma-assocd., Melan-A/MART-1; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Transferrins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(melanotransferrins; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Chromosome
(minichromosomes; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Chemicals
(modification; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Mucins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mucin 2, 3 and 4; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Functional groups
(myristyl; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT DNA
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(naked; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Mammary gland
Prostate gland
(neoplasm; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Microorganism
(non-pathogenic; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Liquids
(oils formulation; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(oral; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(p15; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Functional groups
(palmitoyl; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(parenterals; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(peritoneal; weak antigens inserted with foreign T cell epitope as

vaccines)
IT Glycolipoproteins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphatidylinositol-contg.; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(probasins; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Glycoproteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prostateins; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Interleukin 13
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(receptors; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(self; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(spinal; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(subdermal; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Drug delivery systems
(sublingual; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Mutation
(substitution; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(surface; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(terminator; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Toxoids
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetanus, epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transfection-facilitating; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Proteins, specific or class
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(transmembrane, mesothelin; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Antigens

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., G250; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., GAGE; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., KIAA0205 bladder carcinoma antigen; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., MAP17; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., MIC A/B; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., MUM-1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., NY-ESO-1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., PRAME; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., Pmel-17; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., RCAS1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., ZAG; weak antigens inserted with foreign T cell epitope
as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd., p16INK4; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-assocd.; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antigens
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tumor-rejection, RAGE-1; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Complement receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type 1; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Complement receptors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(type 2; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Animal
Animal cell line
Antigen-presenting cell
Antitumor agents
Bacteriophage
Carriers
Cosmids
DNA sequences
Dendritic cell
Encapsulation
Epitopes
Immunotherapy
Influenza virus
Latex
Liposomes
Macrophage
Micelles
Molecular cloning
Mycobacterium
Particles
Plasmids
Plasmodium falciparum
Protein sequences
Quillaja saponaria
Vaccines
Virus
Virus vectors
(weak antigens inserted with foreign T cell epitope as **vaccines**)
IT Gene, animal
Promoter (genetic element)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(weak antigens inserted with foreign T cell epitope as **vaccines**)
IT CA 125 (carbohydrate antigen)
CD19 (antigen)
CD20 (antigen)
CD22 (antigen)
CD44 (antigen)
CD45 (antigen)
CD5 (antigen)
CD59 (antigen)
Carcinoembryonic antigen
Enzymes, biological studies
Epidermal growth factor receptors
Haptens
.alpha.-Fetoproteins

RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Antibodies
Antigens
CD40 (antigen)
CTLA-4 (antigen)
Calreticulin
Carbohydrates, biological studies
Cytokines
DNA
Heat-shock proteins
Insulin-like growth factor I receptors
Interleukin 1
Interleukin 12
Interleukin 13
Interleukin 15
Interleukin 2
Interleukin 4
Interleukin 6
Ki-67 antigen
Lipid A
Lipids, biological studies
Osteonectin
Plastics, biological studies
Platelet-derived growth factors
Polymers, biological studies
Receptors
Saponins
Toxins
Tumor necrosis factors
neu (receptor)
p53 (protein)
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.alpha.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Catenins
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Transforming growth factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT Interferons
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 39391-18-9
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(2; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 62031-54-3, FGF
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(8a and 8b isoforms; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 264178-47-4P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(P2 epitope gene; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 126779-13-3P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(P2 epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 264185-70-8P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(P30 epitope gene; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 126779-14-4P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(P30 epitope; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 99-20-7D, Trehalose, diester 7429-90-5, Aluminum, biological studies 9004-54-0, Dextran, biological studies 9005-25-8, Starch, biological studies 25322-68-3 53678-77-6, Muramyl dipeptide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**adjuvant**; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 148997-75-5, Androgen-induced growth factor (mouse clone pSC17 precursor reduced) 264179-58-0 264179-59-1, Neu (receptor) (human) 264179-62-6
264179-64-8 264179-65-9 264179-66-0 264179-67-1 264179-68-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 3458-28-4, Mannose 9036-88-8, Mannan
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(binding partner; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT 56093-23-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fusion with LDL receptor; weak antigens inserted with foreign T cell epitope as **vaccines**)

IT **125978-95-2, Nitric oxide** synthase
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inducible; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 9030-23-3, Thymidine phosphorylase
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 141907-41-7, Matrix metalloproteinase
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isoforms; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 100040-73-1, DNA (human clone .lambda.HER2-436 gene HER2 receptor cDNA) 264179-57-9 264179-60-4 264179-61-5 264179-63-7
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(nucleotide sequence; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 52-90-4, Cysteine, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(residue; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 264134-70-5P 264134-71-6P 264134-72-7P 264134-73-8P 264134-78-3P 264224-61-5P 264224-76-2P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 71965-46-3, Cathepsins 99085-47-9, Complement decay-accelerating factor 147014-97-9, Cyclin-dependent kinase 4 179241-78-2, Caspase 8
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 251541-10-3, Human Her2 protein (59-73) 251542-12-8, Human Her2 protein (465-479) 264617-99-4, Human PSM (87-108) 264618-03-3, Human PSM (210-230) 264618-06-6, Human PSM (269-289) 264618-07-7, Human PSM (298-324) 264618-08-8, Human PSM (442-465) 264618-09-9, Human PSM (488-514) 264618-23-7, Human PSM (598-630) 264619-18-3, Human PSM (643-662) 264619-84-3, Human PSM (672-699) 264620-57-7, Human Her2 protein (5-25) 264620-84-0, Human Her2 protein (103-117) 264621-04-7, Human Her2 protein (149-163) 264621-94-5, Human Her2 protein (210-224) 264622-06-2, Human Her2 protein (250-264) 264622-08-4, Human Her2 protein (325-339) 264622-09-5, Human Her2 protein (369-383) 264622-23-3, Human Her2 protein (579-593) 264624-69-3, Human Her2 protein (632-652) 264624-79-5, Human Her2 protein (653-667) 264624-80-8, Human Her2 protein (661-675) 264625-23-2, Human Her2 protein (695-709) 264625-25-4, Human Her2 protein (72-86) 264625-36-7, Human Her2 protein (146-160) 264625-37-8, Human Her2 protein (221-235) 264625-38-9, Human Her2 protein (257-271) 264625-51-6, Human FGF8b protein (1-54) 264626-02-0, Human FGF8b protein (55-58) 264626-17-7, Human FGF8b protein (178-215) 264626-69-9, Human FGF8b protein (63-68) 264626-82-6, Human FGF8b protein (72-76) 264626-84-8, Human FGF8b protein (85-91) 264626-85-9, Human FGF8b protein (95-102) 264626-86-0,

Human FGF8b protein (106-111) 264626-87-1, Human FGF8b protein (115-120)
264627-05-6, Human FGF8b protein (128-134) 264627-07-8, Human FGF8b protein (138-144) 264627-09-0, Human FGF8b protein (149-154)
264627-10-3, Human FGF8b protein (158-162) 264627-11-4, Human FGF8b protein (173-177) 264627-12-5, Human FGF8b protein (26-45)
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**
)
IT 3700-67-2 9001-91-6, Plasminogen 9002-10-2, Tyrosinase 9002-61-3, Human chorionic gonadotropin 9032-22-8, Mox1 oxidase 9034-40-6, Gonadotropin-releasing hormone 9081-34-9, 5.alpha. Reductase 50812-37-8, Glutathione S-transferase 60748-06-3, Gastrin 17 62010-37-1, GD3 65988-71-8, GD2 66456-69-7, GM4 66594-14-7, Quil A 80043-53-4, Gastrin-releasing peptide 83588-90-3, N-Acetylglucosaminyltransferase V 83869-56-1, GM-CSF 89800-66-8, Heparanase 120178-12-3, Telomerase 127464-60-2, Vascular endothelial growth factor 140208-23-7, Plasminogen activator inhibitor-1 141256-04-4, QS21
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(weak antigens inserted with foreign T cell epitope as **vaccines**
)
IT 61512-21-8, Thymosin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.beta. 15; weak antigens inserted with foreign T cell epitope as **vaccines**)
IT 9005-80-5, Inulin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(.gamma.-; weak antigens inserted with foreign T cell epitope as **vaccines**)

L37 ANSWER 5 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:144722 HCAPLUS
DN 132:185454
TI Use of anti-angiogenic agents for inhibiting vessel wall injury
IN Brown, Charles L., III; Gorlin, Steve
PA Global Vascular Concepts, Inc., USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000010552	A2	20000302	WO 1999-US19218	19990824
	WO 2000010552	A3	20001123		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9956871 A1 20000314 AU 1999-56871 19990824
PRAI US 1998-97579 19980824
WO 1999-US19218 19990824
AB Use of anti-angiogenic agents to inhibit an undesirable response to vessel
wall injury, including stent neointima, dialysis graft neointima, vascular
graft-induced neointima, and the treatment of benign hypertrophic scar formation as well as the treatment and passivation of unstable atherosclerotic plaques are provided. The invention provides for the use of catheter-based devices for enhancing the local delivery of anti-angiogenic agents into the endothelial tissues of blood vessels of the living body.
IC ICM A61K031-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
IT Interleukin 1
Interleukin 12
Leukemia inhibitory factor
Protamines
Retinoids
Thrombospondins
Tumor necrosis factors
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-angiogenic agents for inhibiting vessel wall injury)
IT 50-28-2, Estradiol, biological studies 50-35-1, Thalidomide 50-81-7D, Ascorbic acid, ethers 52-01-7, Spironolactone 53-05-4, Tetrahydrocortisone 53-86-1, Indomethacin 60-33-3, Linoleic acid, biological studies 60-54-8, Tetracycline 68-96-2, 17.alpha.-Hydroxyprogesterone 128-13-2, Ursodeoxycholic acid 145-63-1, Suramin 152-58-9, Cortexolone 302-79-4, Retinoic acid 362-07-2, 2-Methoxyestradiol 446-72-0, Genistein 465-21-4, Bufalin 566-35-8 2609-46-3, Amiloride 4431-00-9, Aurine tricarboxylic acid 10118-90-8, Minocycline 12772-57-5, Radicicol 19545-26-7, Wortmannin 33069-62-4,
Taxol 34031-32-8, Auranofin 37270-94-3, Platelet factor 4 38096-31-0, Diaminoanthraquinone 38194-50-2, Sulindac 50903-99-6, **L-Name** 53902-12-8, Tranilast 57381-26-7, Irsogladine 62571-86-2, Captopril 62996-74-1, Staurosporine 65646-68-6, Fenretinide 70563-58-5, Herbimycin A 79831-76-8, Castanospermine 86090-08-6, Angiostatin 100827-28-9, Erbstatin 103909-75-7, 22-Oxa-1.alpha.-25-dihydroxyvitamin D3 105219-56-5, WEB 2086 110124-55-5, MDL 27032 125697-92-9, Lavendustin A 126509-46-4, Eponemycin 129298-91-5, TNP-470 130370-60-4, BB-94 134633-29-7, Tecogalan sodium 142186-14-9, FR-118487 148717-90-2, Squalamine 154039-60-8, Marimastat 171784-03-5, Louisianine A 171784-04-6, Louisianine B 171784-06-8, Louisianine D 187888-07-9, Endostatin 188417-67-6, CM 101 204005-46-9, SU5416
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-angiogenic agents for inhibiting vessel wall injury)

L37 ANSWER 6 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:15159 HCAPLUS
DN 132:73642
TI Acyl pseudodipeptides, preparation method, pharmaceutical compositions containing them for therapeutic use
IN Bauer, Jacques; Martin, Olivier Richard

PA Om Pharma, Switz.
SO PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DT Patent
LA French
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000000462	A1	20000106	WO 1999-IB1170	19990623

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9942848	A1	20000117	AU 1999-42848	19990623

PRAI WO 1998-FR1396 19980630
WO 1999-IB1170 19990623
OS MARPAT 132:73642
AB The invention discloses N-acyl pseudodipeptides XA(CH2)mCH(NHR1)(CH2)nCONH(CH2)pCH(NHR2)(CH2)qBY [R1, R2 = (un)satd. (un)branched (un)substituted C2-24 carboxylic acid; m, p, q = 1-10; n = 0-10; X, Y = H, phosphono, hydroxysulfonyl, dimethoxyphosphoryl, (C1-5 alkyl) carboxy, etc.; A, B = O, S, NH] and salts thereof. The invention also discloses pharmaceutical compns. contg. as active principle at least one of the above compds. The compds. have interesting pharmacol. properties which make them useful as medicines esp. as immunomodulators. The compds. are of interest in the treatment of immune deficiency diseases and diseases involving hyperimmune response, in the treatment of cancer, and as vaccine adjuvants. Their amphiphilic character makes them useful in drug delivery systems.
IC C07C237-00
CC 1-7 (Pharmacology)
Section cross-reference(s): 15, 34, 63
IT Antitumor agents
Dendritic cell
Drug delivery systems
Immunomodulators
Lymphocyte
Macrophage
Monocyte
Protective groups
Reducing agents
Vaccines
(acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)
IT Immunostimulants
(**adjuvants**; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)
IT Proteins, specific or class
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)

(p70, **IL-12**; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)
IT **Interleukin 12**
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(p70; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)
IT **10102-43-9, Nitric oxide**, biological studies
RL: BPR (Biological process); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(macrophage; acyl pseudodipeptide prepn. and pharmaceutical compns. for therapeutic use)
RE.CNT 7
RE
(1) Dai Ichi Seiyaku Co Ltd; JP 61227586 A 1986 HCAPLUS
(2) Gwynfor, D; WO 9514026 A 1995 HCAPLUS
(3) Miyajima, K; Chem Pharm Bull 1997, V45(6), P1089 HCAPLUS
(4) Miyajima, K; Chem Pharm Bull 1997, V45(2), P312 HCAPLUS
(5) Suhara, Y; Chem Pharm Bull 1994, V42(12), P2526 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

Dai's should be 9/13/98

L37 ANSWER 7 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:466559 HCAPLUS
DN 133:191684
TI **Interleukin-12** (**IL-12**) enhancement of the cellular immune response against human immunodeficiency virus type 1 env antigen in a DNA prime/vaccinia virus boost **vaccine** regimen is time and dose dependent: suppressive effects of **IL-12** boost are mediated by **nitric oxide**
AU Gherardi, M. Magdalena; Ramirez, Juan C.; Esteban, Mariano
CS Department of Molecular and Cellular Biology, Centro Nacional de Biotecnologia, CSIC, Universidad Autonoma, Madrid, E-28049, Spain
SO J. Virol. (2000), 74(14), 6278-6286
CODEN: JOVIAM; ISSN: 0022-538X
PB American Society for Microbiology
DT Journal
LA English
AB The authors previously demonstrated that codelivery of interleukin-12 (IL-12) with the human immunodeficiency virus type 1 (HIV-1) Env antigen from a recombinant vaccinia virus (rVV) can enhance the specific anti-Env cell-mediated immune (CMI) response. Here, they investigated the effects of IL-12 in mice when it is expressed in a DNA prime/VV boost vaccine regimen. The delivery of IL-12 and Env product during priming with a DNA vector, followed by a booster with VV expressing the Env gene (rVVenv), was found to trigger the optimal CMI response compared with other immunization schedules studied. Significantly, if IL-12 is also delivered as a booster from the viral vector, an impairment of the effects of IL-12 was obsd. involving nitric oxide (NO), since it was overcome by specific inhibitors of inducible NO synthase. NO caused transient immunosuppression rather than impairment of viral replication. Moreover, at certain viral doses, coadministration of the NO inhibitor during the booster resulted in IL-12-mediated enhancement of the specific CD8+ T-cell response. In addn., the dose of the IL-12-encoding plasmid (pIL-12) and the route of administration of both vectors were relevant factors for

Date is not given

optimal CMI responses. Maximal nos. of Env-specific CD8+ .gamma. interferon-secreting cells were obtained when 50 .mu.g of pIL-12 was administered i.m. at priming, followed by an i.v. rVVenv boost. The authors' results demonstrate, in a murine model, crit. parameters affecting the success of vaccination schedules based on a combination of DNA and VV vectors in conjunction with immunomodulators.

CC 15-2 (Immunochemistry)

ST **interleukin 12** immunomodulation HIV env DNA **vaccine nitric oxide**

IT **Vaccines**
(AIDS; **interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT **Immunostimulants**
(**adjuvants; interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Immunity
(cell-mediated; **interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Human immunodeficiency virus 1
Vaccinia virus
Virus vectors
(**interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Envelope proteins
Interleukin 12
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT DNA
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**vaccine; interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT Anti-AIDS agents
(**vaccines; interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time- and dose-dependent)

IT **10102-43-9, Nitric oxide**, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**interleukin-12** enhancement of cellular immune response against HIV-1 env antigen in DNA prime/vaccinia virus boost **vaccine** regimen is time and dose dependent and **nitric oxide** mediates suppressive effects of **IL-12** boost)

RE.CNT 59

RE

(1) Ahlers, J; J Immunol 1997, V158, P3947 HCAPLUS
(2) Andre, S; J Virol 1998, V72, P1497 HCAPLUS
(5) Boyer, J; Nat Med 1997, V3, P526 HCAPLUS
(7) Caver, T; Vaccine 1999, V17, P1567 HCAPLUS
(8) Chow, Y; J Virol 1997, V71, P169 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 8 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 2000:262313 HCAPLUS
DN 133:72604
TI Direct Immunization of Malaria DNA **Vaccine** into the Liver by Gene Gun Protects against Lethal Challenge of Plasmodium berghei Sporozoite
AU Yoshida, Shigeto; Kashiwamura, Shin-Ichiro; Hosoya, Yoshinori; Luo, Enjie; Matsuoka, Hiroyuki; Ishii, Akira; Fujimura, Akio; Kobayashi, Eiji
CS Department of Medical Zoology, Jichi Medical School, Minamikawachimachi, Tochigi, 329-0498, Japan
SO Biochem. Biophys. Res. Commun. (2000), 271(1), 107-115
CODEN: BBRCA9; ISSN: 0006-291X
PB Academic Press
DT Journal
LA English
AB The liver is the first target organ for malaria parasites immediately after the bite of an infected mosquito. We studied local immunization of malaria DNA vaccines at the site of the liver using a gene gun as a useful tool for in vivo transfection of foreign genes. A malaria DNA vaccine consisting of the Plasmodium berghei circumsporozoite protein (PbCSP) gene plus the mouse IL-12 gene was bombarded directly by a gene gun into mouse liver once or into the skin twice. A marked protective effect was induced by gene bombardment into the liver (more than 71%) compared with that into the skin (less than 33%). A Th1-type immune response and high prodn. of iNOS were obsd. in the hepatic lymphocytes from mice bombarded into the liver, resulting in more effective protection compared with those bombarded into the skin. These results provide an important implication on the development of efficient malaria vaccine strategies. (c) 2000 Academic Press.
CC 15-2 (Immunochemistry)
Section cross-reference(s): 14
ST gene gun malaria **vaccine** Plasmodium IL12
IT **Vaccines**
(antimalarial; gene gun mediated malaria DNA vaccination into liver and protection against lethal challenge of Plasmodium berghei)
IT DNA
Interleukin 12
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(gene gun mediated malaria DNA vaccination into liver and protection against lethal challenge of Plasmodium berghei)
IT Antimalarials
(**vaccines**; gene gun mediated malaria DNA vaccination into liver and protection against, lethal challenge of Plasmodium berghei)

IT **125978-95-2, Nitric oxide** Synthase
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(inducible; gene gun mediated malaria DNA vaccination into liver and protection against lethal challenge of Plasmodium berghei)
RE.CNT 37
RE
(1) Akbari, O; J Exp Med 1999, V189, P169 HCAPLUS
(3) Bharadwaj, A; Infect Immun 1998, V66, P3232 HCAPLUS
(4) Blankenstein, T; Eur J Immunol 1990, V20, P935 HCAPLUS
(6) Doolan, D; J Exp Med 1996, V183, P1739 HCAPLUS
(7) Doolan, D; J Immunol 1999, V163, P884 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 9 OF 25 USPATFULL
AN 1999:84987 USPATFULL
TI Use of **IL-12** and IFN.alpha. for the treatment of infectious diseases
IN Alber, Gottfried, Leipzig, Germany, Federal Republic of
Carr, Jacqueline Anne, Ware, United Kingdom
Mattner, Frank Albert, Mailand, Italy
Mulqueen, Michael John, Rochford, United Kingdom
Palmer, Kathrin, Munchenstein, Switzerland
Rogerson, Jane Andre Louise, St. Albans, United Kingdom
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5928636 19990727
AI US 1997-845973 19970430 (8)
PRAI GB 1996-9932 19960513
DT Utility
EXNAM Primary Examiner: Mertz, Prema
LREP Johnson, George W.; Epstein, William H.; Buchholz, Briana C.
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 629
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a combination of **IL-12** and IFN.alpha. together with a pharmaceutically acceptable carrier useful for treatment and prophylaxis of infectious diseases, preferably chronic infectious diseases and more preferably viral infections, e.g. HSV, HIV, Hepatitis B, Hepatitis C, papilloma etc., bacterial infections, e.g. tuberculosis, salmonellosis, listeriosis, etc., and parasite infections, e.g. malaria, leishmaniasis, and schistosomiasis. These compositions are characterized by the synergistic interaction of **IL-12** and IFN.alpha.. The present invention also provides the use of the above combination for the treatment and prophylaxis of infectious diseases.

L37 ANSWER 10 OF 25 USPATFULL
AN 1999:81550 USPATFULL
TI Recombinant fowlpox viruses and uses thereof
IN Cochran, Mark D., Carlsbad, CA, United States
Junker, David E., San Diego, CA, United States
PA Syntro Corporation, Lenexa, KS, United States (U.S. corporation)
PI US 5925358 19990720
AI US 1995-484575 19950607 (8)
RLI Continuation-in-part of Ser. No. WO 1994-US2252, filed on 28 Feb 1994

which is a continuation of Ser. No. US 1993-24156, filed on 26 Feb 1993,
now abandoned
DT Utility
EXNAM Primary Examiner: Mosher, Mary E.
LREP White, John P.Cooper & Dunham LLP
CLMN Number of Claims: 24
ECL Exemplary Claim: 1
DRWN 11 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 3589
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides a recombinant fowlpox virus comprising a foreign
DNA sequence inserted into the fowlpox virus genomic DNA, wherein the foreign DNA sequence is inserted within a 2.8 kB EcoRI fragment of the fowlpox virus genomic DNA and is capable of being expressed in a fowlpox
virus infected host cell. The invention further provides homology vectors, vaccines and methods of immunization.

L37 ANSWER 11 OF 25 USPATFULL
AN 1999:78766 USPATFULL
TI Methods for in vivo reduction of iron levels and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, United States
PA Medinox, Inc., San Diego, CA, United States (U.S. corporation)
PI US 5922761 19990713
AI US 1996-708552 19960906 (8)
DT Utility
EXNAM Primary Examiner: Criares, Theodore J.
LREP Gray Cary Ware & Freidenrich LLP; Reiter, Stephen E.
CLMN Number of Claims: 40
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1065
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB In accordance with the present invention, there are provided methods for
the in vivo reduction of free iron ion levels in a mammalian subject. The present invention employs a scavenging approach whereby free iron ions are bound in vivo to a suitable physiologically compatible scavenger. The resulting complex renders the free iron ions harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An
exemplary scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-containing composition. This material binds to free iron ions, forming a stable, water-soluble dithiocarbamate-iron complex. The present invention relates to methods for reducing in vivo levels of free iron ions as a means of treating subjects afflicted with iron overload and non-iron overload diseases and/or conditions, such as thalassemia, anemia hereditary hemochromatosis, hemodialysis, stroke and rheumatoid arthritis. Dithiocarbamate-containing scavengers are administered to a host in need
of such treatment; these scavengers interact with in vivo forming a

stable dithiocarbamate-metal complex, which is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo levels of free iron ions.

L37 ANSWER 12 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:194016 HCAPLUS
DN 130:236450
TI Mucosal cytotoxic T lymphocyte responses
IN Berzofsky, Jay A.; Belyakov, Igor M.; Derby, Michael A.; Kelsall, Brian L.; Strober, Warren
PA United States Dept. of Health and Human Services, USA
SO PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9912563	A2	19990318	WO 1998-US19028	19980911
WO 9912563	A3	19990527		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893862	A1	19990329	AU 1998-93862	19980911
EP 1011720	A2	20000628	EP 1998-946965	19980911
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI US 1997-58523 19970911
US 1998-74894 19980217
WO 1998-US19028 19980911

AB The invention provides methods for induction of an antigen-specific, mucosal cytotoxic T lymphocyte response useful in preventing and treating infections with pathogens that gain entry via a mucosal surface. Sol. antigens derived from pathogenic virus or bacteria or protozoan, such as HIV-1, influenza virus, rotavirus, or others are used in cluster peptide vaccine constructs.

IC ICM A61K039-00
ICS A61K039-39; A61K038-19; A61K039-21; A61K039-145; A61K039-02; A61K039-002; A61K009-00; C07K014-16; A61K039-39; A61K038-19

CC 15-2 (Immunochemistry)
Section cross-reference(s): 63

ST mucosal cytotoxic T lymphocyte antigen **vaccine**

IT **Vaccines**
(cluster peptide **vaccine** construct; sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)

IT **Adjuvants** (immunological)
Animal virus
Bacteria (Eubacteria)
CD8-positive T cell
Cat (Felis catus)
Cytotoxic T cell

Drug carriers (drug delivery systems)
Giardia lamblia
Hepatitis A virus
Human immunodeficiency virus
Human immunodeficiency virus 1
Infection
Influenza virus
Listeria monocytogenes
Mammal (Mammalia)
Melanoma
Micelles
Mouse
Pathogen
Primate
Protein sequences
Protozoa
Rotavirus
Surfactants
Viral infection
(sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)

IT Antibodies
Caprylic/capric triglycerides
Cholera toxin
Cytokines
Enamines
Heat labile enterotoxin
Interferon .gamma.
Interleukin 12
Interleukin 2
Interleukin 7
Medium-chain fatty acids
Pertussis toxin
Polyoxyalkylenes, biological studies
Prostate-specific antigen
Protein A
Tumor necrosis factor .alpha.
Tumor-associated antigen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)

IT **10102-43-9, Nitric oxide**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(donor; sol. antigen for induction of mucosal cytotoxic T lymphocyte responses)

date not good

L37 ANSWER 13 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:275426 HCAPLUS
DN 131:72419
TI **Immune-stimulating** complexes induce an **IL-12**-dependent cascade of innate immune responses
AU Smith, Rosemary E.; Donachie, Anne M.; Grdic, Dubravka; Lycke, Nils; Mowat, Allan McI.
CS Department of Immunology, University of Glasgow, Western Infirmary, Glasgow, G11 6NT, UK
SO J. Immunol. (1999), 162(9), 5536-5546
CODEN: JOIMA3; ISSN: 0022-1767

PB American Association of Immunologists
DT Journal
LA English
AB The development of subunit vaccines requires the use of adjuvants that act
by stimulating components of the innate immune response. Immune-stimulating complexes (ISCOMS) contg. the saponin adjuvant Quil A are potential vaccine vectors that induce a wide range of Ag-specific responses in vivo encompassing both humoral and CD4 and CD8 cell-mediated immune responses. ISCOMS are active by both parenteral and mucosal routes, but the basis for their adjuvant properties is unknown. Here we have investigated the ability of ISCOMS to recruit and activate innate immune responses as measured in peritoneal exudate cells. The i.p. injection of ISCOMS induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes. Many of the recruited cells had phenotypic evidence of activation and secreted a no. of inflammatory mediators, including nitric oxide, reactive oxygen intermediates, IL-1, IL-6, IL-12, and IFN-.gamma.. Of the factors that we investigated further
only IL-12 appeared to be essential for the immunogenicity of ISCOMS, as IL-6-and inducible nitric oxide synthase knockout (KO) mice developed normal immune responses to OVA in ISCOMS, whereas these responses were markedly reduced in IL-12KO mice. The recruitment of peritoneal exudate cells following an injection of ISCOMS was impaired in IL-12KO mice, indicating a role for IL-12 in establishing the proinflammatory cascade. Thus, ISCOMS prime Ag-specific immune responses at least in part by activating IL-12-dependent aspects of the innate immune system.
CC 15-2 (Immunochemistry)
ST ISCOM **interleukin 12** innate immune response
IT **Immunostimulants**
(**adjuvants**, ISCOMs; **interleukin-12**
-dependent immune responses induced by ISCOMS)
IT Dendritic cell
Immunostimulation
Lymphocyte
Macrophage
Mast cell
Neutrophil
(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses)
IT Interleukin 1
Interleukin 6
Reactive oxygen species
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses)
IT Inflammation
(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses and inflammation)
IT **Interleukin 12**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**interleukin-12**-dependent immune responses induced by ISCOMS)
IT Interferons
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation,

nonpreparative)
(.gamma.; effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses)
IT 7782-44-7D, Oxygen, reactive species **10102-43-9, Nitric oxide**, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(effect of ISCOMS on immune cells in relation to **interleukin-12**-dependent immune responses)
IT 66594-14-7, Quil A
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**interleukin-12**-dependent immune responses induced by ISCOMS contg. Quil A)
RE.CNT 46
RE
(1) Abdi, K; J Immunol 1997, V159, P3148 HCAPLUS
(2) Albert, M; Nature 1998, V392, P86 HCAPLUS
(3) Baumann, H; Immunol Today 1994, V15, P74 HCAPLUS
(4) Behboudi, S; Clin Exp Immunol 1996, V105, P26 HCAPLUS
(5) Behboudi, S; Cytokine 1997, V9, P682 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 14 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:524711 HCAPLUS
DN 131:270562
TI Immune effector mechanisms in malaria
AU Good, Michael F.; Doolan, Denise L.
CS The Cooperative Research Centre for Vaccine Technology, The Queensland Institute of Medical Research, Queensland, 4029, Australia
SO Curr. Opin. Immunol. (1999), 11(4), 412-419
CODEN: COPIEL; ISSN: 0952-7915
PB Current Biology Publications
DT Journal; General Review
LA English
AB A review with 74 refs. Malaria, a disease responsible for immense human suffering, is caused by infection with Plasmodium spp. parasites, which have a very complex life cycle - antigenically unique stages infect different tissues of the body. This review details recent developments in our understanding of immunity both to pre-erythrocytic stage antigens and to erythrocytic stage antigens. The former is largely mediated via CD8+ T cells and involves IFN-.gamma., nitric oxide, IL-12 and natural killer cells; the latter varies (in different hosts and with different parasites) but is largely mediated by antibody, helper T cells, nitric oxide and .gamma..delta. T cells. The recent progress towards clin. trials of vaccine candidates against both the pre-erythrocytic stage and erythrocytic stage is also summarized, in particular the use of heterologous prime/boost strategies for the former and the use of MSP1 as a candidate vaccine for the latter.
CC 15-0 (Immunochemistry)
Section cross-reference(s): 14
ST review malaria **vaccine** T lymphocyte cytokine
IT **Vaccines**
(antimalarial; immune effector mechanisms in malaria)

IT Antibodies
Interleukin 12
RL: BAC (Biological activity or effector, except adverse); BOC (Biological
occurrence); BIOL (Biological study); OCCU (Occurrence)
(immune effector mechanisms in malaria)
IT Antimalarials
(**vaccines**; immune effector mechanisms in malaria)
IT **10102-43-9, Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological
occurrence); BIOL (Biological study); OCCU (Occurrence)
(immune effector mechanisms in malaria)
RE.CNT 74
RE
(1) Amante, F; J Immunol 1997, V159, P5535 HCAPLUS
(2) Amante, F; Parasite Immunol 1997, V19, P111 HCAPLUS
(4) Anders, R; Vaccine 1998, V16, P240 HCAPLUS
(5) Berzins, K; Malaria Vaccine Development: A Multi-Immune Response Approach 1996, P105 HCAPLUS
(8) Bull, P; Nat Med 1998, V4, P358 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 15 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:45527 HCAPLUS
DN 130:316478
TI Oral vaccination with **immune stimulating** complexes
AU McI Mowat, Allan; Smith, Rosemary E.; Donachie, Anne M.; Furrie, Elizabeth; Grdic, Dubravka; Lycke, Nils
CS Western Infirmary, Department of Immunology, University of Glasgow, Glasgow, G11 6NT, UK
SO Immunol. Lett. (1999), 65(1,2), 133-140
CODEN: IMLED6; ISSN: 0165-2478
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB There is a need for non-living adjuvant vectors which will induce a full range of local and systemic immune responses to orally administered purified antigens. Here the authors describe the authors' experience with
lipophilic immune stimulating complexes (ISCOMS) contg. the saponin adjuvant Quil A. When given orally, ISCOMS contg. the model protein antigen ovalbumin (OVA) induce a wide range of systemic immune responses, including Th1 and Th2 CD4 dependent activity, class I MHC restricted cytotoxic T-cell responses and local prodn. of secretory IgA antibodies. More recent results indicate that ISCOMS may act partly by enhancing the uptake of protein from the gut. In addn., i.p. injection of ISCOMS recruits and activates many components of the innate immune system, including neutrophils, macrophages, and dendritic cells. In parallel, there is increased prodn. of nitric oxide (NO), reactive oxygen intermediates (ROI), interleukins (IL) 1, 6, 12, and .gamma. interferon (.gamma.IFN). Of these factors, only IL-12 is essential for the immunogenicity of ISCOMS in vivo, as mucosal and systemic responses to ISCOMS are reduced in IL-12KO mice, but not in IL-4KO, IL-6KO, inducible NO synthase (iNOS) KO, or .gamma.IFN receptor KO mice. The authors propose that ISCOMS act by targeting antigen and adjuvant to macrophages and/or dendritic cells. This pathway may be amenable to exploitation for

vaccine development, esp. if combined with another vector with a different
mucosal adjuvant profile, such as cholera toxin.
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 15
ST oral **vaccine** mucosal immunity ISCOM
IT **Interleukin 12**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(formation by inflammatory cell in recruitment by mucosal immunogenicity of ISCOMS)
IT Oral **vaccines**
(mucosal immunogenicity of ISCOMS is assocd. with increased antigen uptake by intestine and inflammatory cell recruitment in relation to)
IT **10102-43-9, Nitric oxide**, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(formation by inflammatory cell in recruitment by mucosal immunogenicity of ISCOMS)
RE.CNT 33
RE
(1) Banchereau, J; Nature 1998, V392, P245 HCAPLUS
(3) Claassen, I; Adv Exp Med Biol 1995, V371B, P1485 HCAPLUS
(4) Claassen, I; Eur J Immunol 1995, V25, P1446 HCAPLUS
(5) Cox, J; Vaccine Design: the Role of Cytokine Networks 1997, V293, P33 HCAPLUS
(7) Erturk, M; J Gen Virol 1989, V70, P2149 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 16 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1999:294972 HCAPLUS
DN 131:143293
TI Mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression
AU Koblish, Holly Kurzawa
CS Univ. of Pennsylvania, Philadelphia, PA, USA
SO (1998) 123 pp. Avail.: UMI, Order No. DA9913484
From: Diss. Abstr. Int., B 1999, 59(11), 5772
DT Dissertation
LA English
AB Unavailable
CC 15-5 (Immunochemistry)
ST **interleukin 12** antitumor immunosuppression cancer **vaccine; nitric oxide** inhibitor tumor **vaccine adjuvant**
IT **Vaccines**
(cancer; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)
IT Antitumor agents
(effect; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)
IT Immunosuppression
(mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)
IT **Interleukin 12**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)
IT Neoplasm
(**vaccine**; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)
IT **10102-43-9, Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor; mechanism and control of recombinant murine **interleukin-12**-induced immunosuppression)

L37 ANSWER 17 OF 25 USPATFULL
AN 1998:154309 USPATFULL
TI Method for in vivo reduction of **nitric oxide** levels and compositions useful therefor
IN Lai, Ching-San, Encinitas, CA, United States
PA MCW Research Foundation, Milwaukee, WI, United States (U.S. corporation)
PI US 5847004 19981208
AI US 1996-767125 19961209 (8)
RLI Continuation-in-part of Ser. No. US 1995-554196, filed on 6 Nov 1995 which is a continuation-in-part of Ser. No. US 1995-459518, filed on 2 Jun 1995, now patented, Pat. No. US 5741815
DT Utility
EXNAM Primary Examiner: Rotman, Alan L.; Assistant Examiner: Smith, Lyman H.
LREP Gray Cary Ware and Freidenrich; Reiter, Stephen E.
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1485
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB In accordance with the present invention, there are provided methods for the in vivo reduction of **nitric oxide** levels in a mammalian subject. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for **nitric oxide** production is inhibited), the present invention employs a scavenging approach whereby overproduced **nitric oxide** is bound in vivo to a suitable **nitric oxide** scavenger. The resulting complex renders the **nitric oxide** harmless, and is eventually excreted in the urine of the host. An exemplary **nitric oxide** scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble NO-containing complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy. The present invention relates to methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. **Nitric oxide** scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable NO-containing complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject,

thereby reducing in vivo .NO levels.

L37 ANSWER 18 OF 25 USPATFULL
AN 1998:57964 USPATFULL
TI Methods for in vivo reduction of **nitric oxide** levels and compositions useful therefor
IN Lai, Ching-San, Brookfield, WI, United States
PA MCW Research Foundation, Inc., Milwaukee, WI, United States (U.S. corporation)
PI US 5756540 19980526
AI US 1995-459518 19950602 (8)
DT Utility
EXNAM Primary Examiner: Nazario-Gonzalez, Porfirio
LREP Pretty, Schroeder, Brueggemann & Clark; Reiter, Stephen E.
CLMN Number of Claims: 39
ECL Exemplary Claim: 1,2,14
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1409
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB In accordance with the present invention, there are provided methods for the in vivo reduction of **nitric oxide** levels in a mammalian subject. In contrast to the inhibitory approach described in the prior art (i.e., wherein the function of the enzymes responsible for **nitric oxide** production is inhibited), the present invention employs a scavenging approach whereby overproduced **nitric oxide** is bound in vivo to a suitable **nitric oxide** scavenger. The resulting complex renders the **nitric oxide** harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary **nitric oxide** scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-ferrous iron complex. The present invention relates to methods for reducing in vivo levels of .multidot.NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. Dithiocarbamate-containing **nitric oxide** scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .multidot.NO, forming a stable dithiocarbamate-metal-NO complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo .multidot.NO levels.

L37 ANSWER 19 OF 25 USPATFULL
AN 1998:42383 USPATFULL
TI Methods for in vivo reduction of **nitric oxide** levels and compositions useful therefor
IN Lai, Ching-San, 17765 Bolter La., Brookfield, WI, United States 53045
PI US 5741815 19980421
AI US 1995-554196 19951106 (8)
RLI Continuation-in-part of Ser. No. US 1995-459518, filed on 2 Jun 1995
DT Utility
EXNAM Primary Examiner: Ivy, C. Warren; Assistant Examiner: Smith, Lyman H.
LREP Gray Cary Ware & Freidenrich; Reiter, Stephen E.

CLMN Number of Claims: 41
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1537
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention employs a scavenging approach whereby overproduced **nitric oxide** is bound in vivo to a suitable **nitric oxide** scavenger. The resulting complex renders the **nitric oxide** harmless, and is eventually excreted in the urine of the host. Further in accordance with the present invention, there are provided compositions and formulations useful for carrying out the above-described methods. An exemplary **nitric oxide** scavenger contemplated for use in the practice of the present invention is a dithiocarbamate-ferrous iron complex. This complex binds to .NO, forming a stable, water-soluble dithiocarbamate-iron-NO complex having a characteristic three-line spectrum (indicative of a mononitrosyl-Fe complex) which can readily be detected at ambient temperatures by electron paramagnetic resonance (EPR) spectroscopy. The present invention relates to methods for reducing in vivo levels of .NO as a means of treating subjects afflicted with inflammatory and/or infectious disease. Dithiocarbamate-containing **nitric oxide** scavengers are administered to a host in need of such treatment; these scavengers interact with in vivo produced .NO, forming a stable dithiocarbamate-metal-NO complex. The NO-containing complex is then filtered through the kidneys, concentrated in the urine, and eventually excreted by the subject, thereby reducing in vivo .NO levels.

L37 ANSWER 20 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:717539 HCAPLUS
DN 130:80197
TI Immune suppression by recombinant interleukin (rIL)-12 involves interferon .gamma. induction of **nitric oxide** synthase 2 (iNOS) activity: inhibitors of **NO** generation reveal the extent of rIL-12 **vaccine adjuvant** effect
AU Koblish, Holly Kurzawa; Hunter, Christopher A.; Wysocka, Maria; Trinchieri, Giorgio; Lee, William M. F.
CS Cell and Molecular Biology Graduate Group, Cancer Center, and Institute for Human Gene Therapy, School of Medicine, University of Pennsylvania, Philadelphia, PA, 19104, USA
SO J. Exp. Med. (1998), 188(9), 1603-1610
CODEN: JEMEAV; ISSN: 0022-1007
PB Rockefeller University Press
DT Journal
LA English
AB Recombinant interleukin 12 (IL-12) can profoundly suppress cellular immune responses in mice. To define the underlying mechanism, recombinant murine (rm)IL-12 was given to C57BL/6 mice undergoing alloimmunization and found to transiently but profoundly suppress in vivo and in vitro allogeneic responses and in vitro splenocyte mitogenic responses. Use of neutralizing antibodies and genetically deficient mice showed that

IFN-.gamma. (but not TNF-.alpha.) mediated rmIL-12-induced immunosuppression. Splenocyte fractionation studies revealed that adherent cells from rmIL-12-treated mice suppressed the mitogenic response of normal nonadherent cells to Con A and IL-2. Addn. of an inhibitor of nitric oxide synthase (NOS) restored mitogenic responses, and inducible (i)NOS-/- mice were not immunosuppressed by rmIL-12. These results support the view that suppression of T cell responses is due to NO produced by macrophages responding to the high levels of IFN-.gamma. induced by rmIL-12. When a NOS inhibitor was given with rmIL-12 during vaccination of A/J mice with irradiated SCK tumor cells, immunosuppression was averted and the extent of rmIL-12's ability to enhance induction of protective antitumor immunity was revealed. This demonstrates that rmIL-12 is an effective vaccine adjuvant whose efficacy may be masked by its transient immunosuppressive effect.

CC 15-5 (Immunochemistry)

ST immunosuppression **interleukin 12** interferon gamma **nitric oxide** synthase; **vaccine adjuvant interleukin 12** immunosuppression

IT **Vaccines**
(antitumor; **interleukin-12 vaccine adjuvant** effect as revealed by inhibition of **nitric oxide** formation)

IT Immunosuppression
(immunosuppression by **interleukin-12** involves interferon .gamma. induction of **nitric oxide** synthase 2)

IT **Interleukin 12**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(immunosuppression by **interleukin-12** involves interferon .gamma. induction of **nitric oxide** synthase 2)

IT Interferon .gamma.
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(immunosuppression by **interleukin-12** involves interferon .gamma. induction of **nitric oxide** synthase 2)

IT **Adjuvants** (immunological)
(**interleukin-12 vaccine adjuvant** effect as revealed by inhibition of **nitric oxide** formation)

IT **125978-95-2, Nitric oxide** synthase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(2; immunosuppression by **interleukin-12** involves interferon .gamma. induction of **nitric oxide** synthase 2)

IT **10102-43-9, Nitric oxide**, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(immunosuppression by **interleukin-12** involves interferon .gamma. induction of **nitric oxide** synthase 2)

RE.CNT 31

RE

(1) Atkins, M; Clin Cancer Res 1997, V3, P409 HCAPLUS
(2) Bingisser, R; J Immunol 1998, V160, P5729 HCAPLUS
(3) Brunda, M; Res Immunol 1995, V146, P622 HCAPLUS
(4) Candolfi, E; Infect Immun 1994, V62, P1995 HCAPLUS
(5) Candolfi, E; Infect Immun 1995, V63, P751 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 21 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:503172 HCAPLUS
DN 129:215611
TI Control of **IL-12** and IFN-.gamma. production in response to live or dead bacteria by TNF and other factors
AU Zhan, Yifan; Cheers, Christina
CS Department Microbiology, University Melbourne, Parkville, 3055, Australia
SO J. Immunol. (1998), 161(3), 1447-1453
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB When mice were infected i.v. with either Listeria monocytogenes or Brucella abortus, bioactive IL-12 was briefly detected in serum and supernatants of spleen homogenates immediately ex vivo. Although the time scale was more prolonged for the more slowly growing B. abortus, in both instances IL-12 prodn. ceased while bacteria still persisted in high nos. Prodn. of IL-12, detected in serum and spleen, was neither increased nor prolonged by injecting Abs to IL-10 or IL-4. In contrast with live organisms, heat-killed bacteria did not induce detectable IL-12 in vivo and were less efficient when added in vitro to resident peritoneal cells or spleen cells. Mice lacking the receptors for TNF (TNFR-/- mice) were severely deficient in IL-12 prodn., suggesting a controlling role for TNF, which the authors have previously shown to be triggered by live, rather than dead, bacteria. Infection in the TNFR-/- mice was exacerbated, although in the Brucella-infected mice splenomegaly, the main indicator of immunopathol., was reduced. Prodn. of NO by macrophages was deficient, but the TNFR-/- mice were not deficient in IFN-.gamma. prodn. In addn. to being poor inducers of IL-12, killed bacteria actively suppressed IL-12 prodn. in response to live bacteria, by mechanism(s) unknown. The implications of these findings are discussed in light of the fact that only live bacteria satisfactorily induce cell-mediated immunity to infection.
CC 15-8 (Immunochemistry)
ST **interleukin 12** live dead bacteria TNF; interferon gamma live dead bacteria TNF; tumor necrosis factor cytokine bacterial infection
IT Bacterial infection
Brucella melitensis
Listeria monocytogenes
(**interleukin-12** and interferon .gamma. formation control in response to live or dead bacteria by tumor necrosis factor)
IT Tumor necrosis factors
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**interleukin-12** and interferon .gamma. formation

control in response to live or dead bacteria by tumor necrosis factor)
IT Interferon .gamma.
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** and interferon .gamma. formation
control in response to live or dead bacteria by tumor necrosis factor)
IT **Interleukin 12**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** and interferon .gamma. formation
control in response to live or dead bacteria by tumor necrosis factor)
IT **Vaccines**
(**interleukin-12** and interferon .gamma. formation
control in response to live or dead bacteria by tumor necrosis factor
in relation to)
IT **10102-43-9, Nitric oxide**, biological studies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** and interferon .gamma. formation
control in response to live or dead bacteria by tumor necrosis factor)

L37 ANSWER 22 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1998:571676 HCAPLUS
DN 129:314792
TI Expression of cytokine genes in Aotus monkeys immunized with synthetic and
recombinant Plasmodium vivax and P. falciparum antigens
AU Duque, S.; Montenegro-James, S.; Arevalo-Herrera, M.; Praba, A. D.; Villinger, F.; Herrera, S.; James, M. A.
CS Instituto Nacional de Salud, Bogota, Colombia
SO Ann. Trop. Med. Parasitol. (1998), 92(5), 553-559
CODEN: ATMPA2; ISSN: 0003-4983
PB Carfax Publishing Ltd.
DT Journal
LA English
AB Cytokine responses in human host-protective immunity to malaria have yet to be completely elucidated. No data appear to exist on the cytokine patterns in non-human primate models immunized with malarial antigens. Expression of mRNA transcripts of 10 cytokines, the adhesion mol. ICAM-1, and inducible nitric oxide synthase (iNOS) in peripheral-blood mononuclear
cells (PBMC) from 9 Aotus monkeys was analyzed by reverse-transcriptase PCR. Five of the monkeys had been immunized with multiple-antigen peptides (MAP) of the P. vivax circumsporozoite protein and 2 with constructs of the P. falciparum merozoite surface protein-1 (MSP-1). The other 2 monkeys served as non-immunized controls. PBMC were cultured for 24 h after stimulation with phytohemagglutinin mitogen, MAP, and MSP-1 antigens. Elevated expression of interleukin-6 (IL-6), IL-10, IL-12, tumor necrosis factor-.alpha. (TNF-.alpha.), TNF-.beta., and iNOS was seen
in response to the MAP. Monkeys immunized with either P. falciparum MSP r190L or synthetic 190L peptides expressed predominantly the type-1 cytokines (IL-1.beta., IL-12, interferon-.gamma., TNF-.alpha., TNF-.beta.)
characteristic of splenic, cell-mediated activity with macrophage activation and nitric oxide prodn.
CC 15-5 (Immunochemistry)

IT Aotus
Gene expression
Malaria **vaccines**
Plasmodium falciparum
Plasmodium vivax
(cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

IT **Interleukin 12**
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

IT **10102-43-9**, Nitrogen oxide (**NO**), biological studies
83869-56-1, GM-CSF
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

IT **125978-95-2, Nitric oxide** synthase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inducible; cytokine genes expression in Aotus monkeys immunized with synthetic and recombinant Plasmodium vivax and P. falciparum antigens)

L37 ANSWER 23 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:696638 HCAPLUS
DN 128:727
TI DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy
IN Prendergast, Patrick T.
PA Prendergast, Patrick T., Ire.
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9738695	A1	19971023	WO 1997-IB414	19970417
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	CA 2251733	AA	19971023	CA 1997-2251733	19970417
	AU 9725741	A1	19971107	AU 1997-25741	19970417
	EP 901375	A1	19990317	EP 1997-917365	19970417
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	CN 1216470	A	19990512	CN 1997-193912	19970417
	JP 2000508654	T2	20000711	JP 1997-536909	19970417
	WO 9847516	A1	19981029	WO 1997-EP5716	19971016
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,				

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
GN, ML, MR, NE, SN, TD, TG

	AU 9852219	A1	19981113	AU 1998-52219	19971016
	NO 9804851	A	19981217	NO 1998-4851	19981016

PRAI US 1996-15695 19960417
WO 1970-IB414 19970417
WO 1997-IB414 19970417
WO 1997-EP5716 19971016
OS MARPAT 128:727
AB There are provided medicaments, methods of making them, and kits, which include (1) a 17-ketosteroid compd. and/or (2) anti-serum either poly- or monoclonal to Interleukin 10, Interleukin 2, or Interleukin 12, or with any compd. which can effectively inhibit synthesis or the biol. function of Interleukin 10, Interleukin 12, or Interleukin 2, or with an Interleukin 10, Interleukin 12, or Interleukin 2 receptor mol.-blocking agent, or with anti-serum, either polyclonal or monoclonal to human .alpha.-fetoprotein. There are also provided methods of treatment involving such compds. or combinations of compds., including enhancing Th1 immune protective responses when using the 17-ketosteroid compd. as an anti-viral, anti-bacterial, anti-mycoplasm or anti-intracellular parasitic agent.
IC ICM A61K031-565
ICS A61K031-70
CC 2-4 (Mammalian Hormones)
Section cross-reference(s): 1, 15, 63
IT AIDS (disease)
Antibacterial agents
Antiserums
Antitumor agents
Antiviral agents
Human immunodeficiency virus
Immunological diseases
Immunosuppressants
Metastasis inhibitors
Multiple sclerosis
Th2 cell
Vaccines
(DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)
IT **Interleukin 12**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibodies to; DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)
IT **Interleukin 12**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(receptors, blockers; DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)
IT 53-43-0, Dhea 446-72-0, Genistein 2219-31-0, L-Canavanine sulfate

14402-89-2, Sodium nitroprusside 17035-90-4, **L-NMMA**
35287-69-5, Secalonic acid d 70563-58-5, Herbimycin A
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DHEA combination therapy with interleukin antibodies for antiviral, antibacterial, antimycoplasmal, or anti-intracellular parasite therapy)

L37 ANSWER 24 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1997:333720 HCAPLUS
DN 127:3837
TI Cellular immune reactions directed against Toxoplasma gondii with special emphasis on the central nervous system
AU Daeubener, Walter; Hadding, Ulrich
CS Institut fur Med. Mikrobiologie und Virologie, Heinrich-Heine-Universitat, Dusseldorf, Dusseldorf, D-40001, Germany
SO Med. Microbiol. Immunol. (1997), 185(4), 195-206
CODEN: MMIYAO; ISSN: 0300-8584
PB Springer
DT Journal; General Review
LA English
AB A review with 133 refs. Toxoplasma gondii is an obligate intracellular parasite which, after primary infection of humans, is maintained in a dormant state by the host cellular immune system. In the event of an acquired immunosuppression, those parasites surviving as dormant cysts in the host may undergo a change in status, proliferate and cause a life-threatening toxoplasmic encephalitis. Over the last decade much knowledge has accumulated concerning the immune response against T. gondii. This review focuses attention particularly on the anti-parasitic effector mechanisms and the cellular immune reactions in the central nervous system during the course of reactivated toxoplasmic encephalitis.
CC 15-0 (Immunochemistry)
Section cross-reference(s): 14
IT Interferon .beta.
Interferon .gamma.
Interleukin 1
Interleukin 10
Interleukin 12
Interleukin 2
Interleukin 4
Interleukin 7
Tumor necrosis factor .alpha.
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cytokines and immunocytes in defense against toxoplasmic encephalitis)
IT **10102-43-9, Nitric oxide**, biological studies
83869-56-1, Granulocyte-macrophage colony-**stimulating** factor
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cytokines and **immunocytes** in defense against toxoplasmic encephalitis)

L37 ANSWER 25 OF 25 HCAPLUS COPYRIGHT 2001 ACS
AN 1996:659868 HCAPLUS
DN 125:299294

TI **IL-12** enhances **vaccine**-induced immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite

AU Wynn, Thomas A.; Reynolds, Alicia; James, Stephanie; Cheever, Allen W.; Caspar, Pat; Hieny, Sara; Jankovic, Dragana; Strand, Mette; Sher, Alan
CS Immunobiol. Section, Natl. Inst. Health, Bethesda, MD, 20892, USA

SO J. Immunol. (1996), 157(9), 4068-4078
CODEN: JOIMA3; ISSN: 0022-1767
DT Journal
LA English

AB The prodn. of Th1-type cytokines is assocd. with strong cell-mediated immunity, while Th2-type cytokines typically dominate humoral immune responses. In mice vaccinated a single time with attenuated cercariae of Schistosoma mansoni, the protection induced is assocd. with Th1 cytokine-dependent, cell-mediated immunity. In contrast, mice vaccinated multiple times display a more Th2-type dominant cytokine response and develop Ab-dependent resistance. We have previously shown that IL-12 enhances cell-mediated immunity in singly vaccinated mice. In the present study, we asked what effects administering IL-12 as an adjuvant would have on the development of a protective humoral response in multiply immunized animals. We found that multiply immunized/IL-12-treated mice displayed a marked increase in resistance to challenge infection, with some animals demonstrating complete protection. The IL-12-vaccinated mice developed strongly polarized Th1 responses but, importantly, also showed significant increases in parasite-specific Ab and, in particular, IgG2a, IgG2b, and IgG1 isotypes. Passive transfer demonstrated an enhanced ability of serum from these animals to protect naive recipients. In addn., animals vaccinated in the presence of IL-12 also developed macrophages with increased nitric oxide-dependent killing activity against the parasites. Together, these data demonstrate that IL-12, initially described as an adjuvant for cell-mediated immunity, may be used to simultaneously promote both humoral and cell-mediated protective responses against infection.

CC 15-8 (Immunochemistry)
ST Schistosoma infection immunity **interleukin 12**

IT Lymphokines and Cytokines
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** enhances cytokine formation by T-cells in relation to immunity to schistosomes)

IT Macrophage
(**interleukin-12** enhances **nitric oxide**-dependent killing of schistosomes by macrophages)

IT Schistosoma mansoni
Vaccines
(**interleukin-12** enhances **vaccine**-induced immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite)

IT Antibodies
RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** enhances **vaccine**-induced

immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite)

IT Lymphocyte
(T-cell, helper cell/inducer, TH1, **interleukin-12** enhances **vaccine**-induced immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite)

IT Lymphokines and Cytokines
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**interleukin 12, interleukin-12** enhances **vaccine**-induced immunity to schistosomes by augmenting both humoral and cell-mediated immune responses against the parasite)

IT **10102-43-9, Nitric oxide**, biological studies
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**interleukin-12** enhances **nitric oxide**-dependent killing of schistosomes by macrophages)

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

ADT WO 2000066720 A2 WO 2000-US11356 20000428
PRAI US 1999-132123 19990430
AB WO 200066720 A UPAB: 20001230
NOVELTY - Protecting pancreatic islet beta -cells from immune system-mediated toxicity comprises transducing the pancreatic islet beta -cells with adeno-associated virus (AAV) vectors into which are inserted genetic materials that encode products that reduce immune system-mediated cell toxicity in the transduced cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) AAV vectors into which are inserted pancreatic islet beta-cell cytoprotective genetic materials; and

(2) preventing rejection of transplanted pancreatic islet beta-cells.

ACTIVITY - Immunosuppressive; antidiabetic.

MECHANISM OF ACTION - Gene therapy; cytoprotective.

No supporting biological data given.

USE - To protect pancreatic islet beta -cells from immune system-mediated toxicity and to prevent rejection of transplanted pancreatic islet beta -cells (claimed). The vectors can be used in gene therapy and also to prevent the development of type I diabetes.

ADVANTAGE - AAV is non-pathogenic because it requires co-infection with a helper virus for productive infection, but does not require co-infection to become integrated into a host cell or to persist in host cells, thus leading to long-term, stable gene expression, even in the non-dividing cells pancreatic beta -cells. The AAV vectors may integrate as multi-copy tandem repeats, unlike retroviral vectors, thus enhancing transgene expression. The small genome of AAV allows for early manipulation by standard recombinant methodology. The use of AAV transduction is advantageous in that DNA polymerase, the enzyme responsible for AAV replication, has a 10,000-fold lower error rate than reverse transcriptase.

Dwg.0/6

L9 ANSWER 2 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-452382 [39] WPIDS
DNC C2000-137931
TI Expression vector comprising multiple shear stress response elements, useful for modulating endothelial cell proliferation, stimulating or down-regulating angiogenesis and treating vasculogenic/angiogenic disorders.
DC B04 D16
IN RESNICK, N
PA (FLOR-N) FLORENCE MEDICAL LTD
CYC 90
PI WO 2000039275 A2 20000706 (200039)* EN 61p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000017954 A 20000731 (200050)

ADT WO 2000039275 A2 WO 1999-IL702 19991223; AU 2000017954 A AU 2000-17954 19991223
FDT AU 2000017954 A Based on WO 200039275
PRAI US 1998-220510 19981224; US 1998-113863 19981224
AB WO 200039275 A UPAB: 20000818
NOVELTY - A vector (I) comprising a multiple number of nucleic acids of promoter Shear Stress Response Elements (SSRE) and one or more genes, or a nucleic acid of an antisense molecule, ribozyme, double stranded RNA, or a nucleic acid which encodes for a repressor antibody, mutant protein which inhibits the synthesis of, or activity of the protein or peptide, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a host cell comprising (I); and

(2) a method for screening (III) test compound for their ability to regulate angiogenesis and/or vasculogenesis, comprising:

(a) contacting endothelial cells with the compound to be tested;

(b) assaying the amount of angiogenesis and/or vasculogenesis produced as a result of the test compound;

(c) stimulating endothelial cells by introducing (I);

(d) assaying the amount of angiogenesis and/or vasculogenesis produced as a result of the vector;

(e) comparing the amount of angiogenesis and/or vasculogenesis produced as a result of (b) to that of (d), where an increased amount of angiogenesis and/or vasculogenesis of the test compound indicates that the test compound regulates angiogenesis and/or vasculogenesis.

ACTIVITY - Cytostatic; Cardiant; Vasotropic; Vulnerary; Antidiabetic; Antiatherosclerotic; Hypotensive; Antilipemic.

MECHANISM OF ACTION - Gene therapy.

No supporting biological data is provided.

USE - (I) is useful for stimulating or inhibiting vascular endothelial cell or capillary endothelial cell proliferation and for stimulating angiogenesis in cells. (I) or (II) is useful for modulating vascular permeability in a mammal, for stimulating or inhibiting the formation, maturation or regression of blood vessels, modulating genes or proteins involved in a diseases, down regulating angiogenesis and for treating vasculogenic and/or angiogenic disorders. These disorders include cardiovascular disorder, neoplastic disorders, ischemia, atherosclerosis, hypertension, diabetes, hypercholesterolemia and wound healing.

(II) is administered to the mammal in the vasculature such that the vasculature has shear stress forces to permit SSRE to be activated by the shear stress and transcriptionally regulate endothelial cell gene expression. Down regulation of angiogenesis further comprises administering an inflammatory agent, vasodilator, fibrinolytic activators, tumor necrosis factor (TNF) or thrombotic factors or an agent which acts as a vasoconstrictor.

(I) is also useful for detecting shear stress or shear stress related condition in a subject, where the reporter gene in (I) is activated in shear stress environment indicating shear stress or its related condition.

SSRE vectors are also useful for screening test compounds for their

ability to regulate angiogenesis and/or vasculogenesis (all claimed). Dwg.0/2

L9 ANSWER 3 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-224531 [19] WPIDS
DNC C2000-068615
TI Method of inhibiting injury to vascular tissue comprising local administration of antiangiogenic agent.
DC B05 D16
IN BROWN, C L; GORLIN, S
PA (GLOB-N) GLOBAL VASCULAR CONCEPTS INC
CYC 87
PI WO 2000010552 A2 20000302 (200019)* EN 29p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 9956871 A 20000314 (200031)
ADT WO 2000010552 A2 WO 1999-US19218 19990824; AU 9956871 A AU 1999-56871 19990824
FDT AU 9956871 A Based on WO 200010552
PRAI US 1998-97579 19980824
AB WO 200010552 A UPAB: 20000419
NOVELTY - A new method of inhibiting injury to vascular tissue comprises local administration of an anti-angiogenic agent.
ACTIVITY - Antiarteriosclerosis; cardiant; vasotropic; antianginal, cerebroprotective; cytostatic.
MECHANISM OF ACTION - None given.
USE - The vascular injury is due to atherosclerosis, cardiac transplant vasculopathy, coronary restenosis following coronary intervention, balloon angioplasty, stent placement, rotablator, carotid endarterectomy, dialysis graft stenosis, graft anastomosis neointima, unstable angina, acute myocardial infarction, stroke, benign hypertrophy or benign prostatic hypertrophy, particularly atheroscerosis or restenosis.
Dwg.0/6

L9 ANSWER 4 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1999-243663 [20] WPIDS
DNC C1999-071033
TI Method for inducing a protective mucosal cytotoxic T lymphocyte immune response.
DC A96 B04 D16
IN BELYAKOV, I M; BERZOFSKY, J A; DERBY, M A; KELSALL, B L; STROBER, W
PA (USSH) US DEPT HEALTH & HUMAN SERVICES; (USSH) US DEPT HEALTH & HUMAN SERVICE
CYC 83
PI WO 9912563 A2 19990318 (199920)* EN 85p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9893862 A 19990329 (199932)

EP 1011720 A2 20000628 (200035) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9912563 A2 WO 1998-US19028 19980911; AU 9893862 A AU 1998-93862 19980911; EP 1011720 A2 EP 1998-946965 19980911, WO 1998-US19028 19980911
FDT AU 9893862 A Based on WO 9912563; EP 1011720 A2 Based on WO 9912563
PRAI US 1998-74894 19980217; US 1997-58523 19970911
AB WO 9912563 A UPAB: 19990525
NOVELTY - A novel method for inducing a protective mucosal cytotoxic T lymphocyte (CTL) response in a mammalian subject comprises contacting a mucosal tissue of the subject with a composition comprising a purified soluble antigen.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a method for inducing a protective mucosal CTL response in a subject comprising contacting a mucosal tissue of the subject with a composition comprising a soluble antigen which does not comprise an adjuvant; and
(2) an immunogenic composition for inducing a protective mucosal CTL response in a subject and adapted for intrarectal administration comprising a purified soluble antigen formulated for intrarectal delivery to the rectum, colon, sigmoid colon or distal colon.
USE - The methods can induce a protective mucosal CTL response in a subject. The method can be used for protection against e.g. hepatitis A virus, papilloma virus, feline immunodeficiency virus, feline leukemia virus, Listeria monocytogenes, M. tuberculosis, M. leprae, or Giardia lamblia.
ADVANTAGE - The method induces long-lasting protective mucosal immune responses.
Dwg.0/17

L9 ANSWER 5 OF 5 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1998-348525 [30] WPIDS
DNC C1998-107826
TI New method for treating or preventing asthma - comprises use of DNA encoding IFN-gamma, IL-10, **IL-12** or **nitric oxide** synthase and DNA for control of expression using a ligand.
DC B04 D16
IN CERASOLI, F
PA (ARIA-N) ARIAD GENE THERAPEUTICS INC
CYC 23
PI WO 9826066 A1 19980618 (199830)* EN 63p
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KR US
AU 9878476 A 19980703 (199847)
EP 948619 A1 19991013 (199947) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 9826066 A1 WO 1997-US22454 19971209; AU 9878476 A AU 1998-78476 19971209; EP 948619 A1 EP 1997-949785 19971209, WO 1997-US22454 19971209
FDT AU 9878476 A Based on WO 9826066; EP 948619 A1 Based on WO 9826066
PRAI US 1996-32260 19961209
AB WO 9826066 A UPAB: 19991122
A method for treating or preventing asthma in a mammal comprising genetically engineered cells, comprises administering to the mammal a ligand. The cells comprise: (a) at least one target DNA construct containing a target gene encoding interferon (IFN)- gamma , interleukin (IL)-10, **IL-12** or **nitric oxide** (
NO) **synthase** operably linked to a heterologous

transcription control element, and (b) at least one DNA construct encoding a transcription regulating protein, which, in the presence of a ligand to which it binds, activates expression of the target gene. Also claimed are:

(1) a method for genetically engineering mammalian cells, to render them capable of regulated expression of a target gene comprising a DNA sequence encoding a target protein selected from IFN- gamma , IL-10, **IL-12**, and **NO synthase**, comprising introducing into the cells a target DNA construct comprising a target gene linked to a transcription control sequence permitting ligand-dependent expression of the target gene, and (2) a method for genetically engineering mammalian cells, to render them capable of ligand dependent expression of a target protein, comprising introducing into the cells: (a) a first DNA construct encoding a chimeric protein comprising: (i) at least one receptor domain capable of binding to the ligand, and (ii) a signal initiation domain, heterologous with respect to the receptor domain, but capable, upon oligomerisation with at least 1 other like domains, of triggering the activation of transcription of a target gene under the transcription control of a transcription control element responsive to the oligomerisation, and (b) a target gene construct comprising a gene encoding a target protein under the expression control of a transcription control element responsive to the oligomerisation; and which following exposure to the ligand, expresses the target gene.

USE - Asthma has been defined as a lung disease characterised by: (i) reversible (not completely in some patients) airway obstruction either spontaneously or with treatment; (ii) airway inflammation, and (iii) increased airway responsiveness to a variety of stimuli. Asthma also has been defined as a chronic inflammatory disorders or the airways in which many cells play a role, including mast cells and eosinophils. In susceptible individuals the inflammation causes symptoms usually associated with widespread but variable airflow obstruction. So, the method can be used for treating or preventing asthma and related disorders.

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     FILE 'REGISTRY' ENTERED AT 10:41:14 ON 22 FEB 2001
                E NITRIC OXIDE/CN
L1              1 S E3
                E NITRIC OXIDE SYNTHASE/CN
L2              1 S E3
                E L-NAME/CN
L3              1 S E3
                E L-NMMA/CN
L4              1 S E3
L5              4 S L1 OR L2 OR L3 OR L4

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L6          51756 S L5
L7          59656 S L6 OR NITRIC OXIDE OR  NO SYNTHASE OR L NAME OR L NMMA
L8           5921 S INTERLEUKIN 12 OR IL12 OR IL 12
L9            254 S L8 AND L7
L10         33309 S ADJUVANT#
L11         62517 S VACCINE#
L12            10 S L10 AND L9
L13             0 S TI 1-10
L14          4726 S L8/IT
L15           203 S L14 AND L7
L16             8 S L15 AND L10
L17            10 S L15 AND L11
L18         15786 S IMMUNOSTIMU? OR IMMUN? (2A) STIMUL?
L19            11 S L18 AND L15
L20            24 S L19 OR L17 OR L16
L21          7652 S L3 OR L4 OR L NAME OR L NMMA
L22             7 S L21 AND L8
L23             7 S L22 NOT L20

     FILE 'BIOSIS' ENTERED AT 10:51:52 ON 22 FEB 2001

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L20 ANSWER 1 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:84465 BIOSIS
DN PREV200100084465
TI Effects of cholera toxin on macrophage production of co-stimulatory cytokines.
AU Cong, Yingzi; Oliver, Alfred O.; Elson, Charles O. (1)
CS (1) Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, 703 S. 19th Street, 633 Zeigler Research Building, Birmingham, AL, 35294-0007: charles-elson@gihep.uab.edu USA
SO European Journal of Immunology, (January, 2001) Vol. 31, No. 1, pp. 64-71.
print.
ISSN: 0014-2980.
DT Article
LA English
SL English
AB Cholera toxin (CT), the enterotoxin of Vibrio cholerae, is a potent mucosal and systemic immunogen and **adjuvant**. The precise mechanism of the adjuvanticity of CT is poorly understood. Our previous work has showed that CT up-regulates B7.2, but not B7.1 expression on macrophages, and thus increases their co-stimulatory activity. In the current study, the effects of CT on macrophage co-stimulatory cytokine production were investigated. Bone marrow macrophages were generated by culturing bone marrow cells with macrophage colony-stimulating factor. CT treatment increased endotoxin-stimulated macrophage IL-10, IL-6, and IL-1beta production, whereas it decreased IL-12, TNF-alpha and **nitric oxide** production. Antibody blocking experiments showed that CT inhibition of IL-12 and TNF-alpha production was mediated by increased IL-10 production, in that addition of anti-IL-10 monoclonal antibody abrogated CT inhibition. The decrease in **nitric oxide** production was in turn secondary to inhibition of TNF-alpha production. Taken together, our study demonstrated that CT has differential effects on various macrophage co-stimulatory cytokines, effects that are likely to contribute to its adjuvanticity.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Infection
IT Parts, Structures, & Systems of Organisms
bone marrow: blood and lymphatics, immune system; macrophage: blood and lymphatics, immune system, production
IT Chemicals & Biochemicals
IL-1-beta [interleukin-1-beta]: production; IL-10 [interleukin-10]: production; **IL-12** [**interleukin-12**]: production; IL-6 [interleukin-6]: production; TNF-alpha [tumor necrosis factor-alpha]: production; cholera toxin: **adjuvant**, enterotoxin, immunogen; macrophage colony-stimulating factor; **nitric oxide**: production
ORGN Super Taxa
Animalia; Vibrionaceae: Facultatively Anaerobic Gram-Negative Rods, Eubacteria, Bacteria, Microorganisms
ORGN Organism Name
Vibrio cholerae (Vibrionaceae): pathogen; animal (Animalia)
ORGN Organism Superterms
Animals; Bacteria; Eubacteria; Microorganisms
RN 81627-83-0 (MACROPHAGE COLONY-STIMULATING FACTOR)
10102-43-9 (**NITRIC OXIDE**)

L20 ANSWER 2 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:50600 BIOSIS
DN PREV200100050600
TI Adherent dendritic cells expressing high levels of interleukin-10 and low levels of interleukin-12 induce antigen-specific tolerance to experimental autoimmune encephalomyelitis.
AU Yang, J.-S.; Xu, L.-Y.; Huang, Y.-M.; Van Der Meide, P. H.; Link, H.; Xiao, B.-G. (1)
CS (1) Karolinska Institute, Division of Neurology, Huddinge University Hospital, Huddinge, S-141 86, Stockholm Sweden
SO Immunology, (November, 2000) Vol. 101, No. 3, pp. 397-403. print. ISSN: 0019-2805.
DT Article
LA English
SL English
AB We have previously shown that tolerance can be induced against acute experimental autoimmune encephalomyelitis (EAE) in Lewis rats by bone marrow-derived dendritic cells (DC) that have been pulsed in vitro with encephalitogenic myelin basic protein peptide 68-86 (MBP 68-86), and injected subcutaneously into healthy rats prior to immunization with MBP 68-86 plus complete Freund's **adjuvant**. To elucidate better the properties of tolerogenic DC, we here compared plastic-adherent DC with floating, non-adherent DC, which were cultured for 7 days in the presence of granulocyte-macrophage colony-stimulating factor plus interleukin-4 (IL-4). Adherent DC expressed high levels of IL-10 mRNA and protein, and low levels of IL-12 mRNA and showed high expression of CD54 compared with floating DC. Proliferation, nitrite concentration and capacity for antigen presentation were lower in adherent DC than in floating DC. There were no differences between adherent and floating DC regarding expression of CD11c, OX62, major histocompatibility complex class II, CD80, or CD86. Most importantly, we observed that adherent DC induced tolerance to EAE in vivo when injected subcutaneously into Lewis rats prior to immunization, while floating DC did not. Adherent DC-mediated tolerance to EAE was associated with augmented proliferation, **nitric oxide** production and frequency of apoptotic cells as well as with up-regulation of transforming growth factor-beta (TGF-beta) -expressing cells in T-cell areas of lymph nodes. Tolerance induction by adherent DC seems to be related to a **nitric oxide**-apoptosis pathway and to upregulation of TGF-beta-expressing cells.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
dendritic cell: immune system
IT Diseases
autoimmune encephalomyelitis: immune system disease
IT Chemicals & Biochemicals
CD11c; CD54; CD80; CD86; OX62; granulocyte-macrophage colony stimulating factor; interleukin-10; **interleukin-12**; interleukin-4; major histocompatibility complex class II; transforming growth factor-beta
IT Alternate Indexing
Encephalomyelitis, Allergic (MeSH)
ORGN Super Taxa

Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rat (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 83869-56-1 (GRANULOCYTE-MACROPHAGE COLONY STIMULATING FACTOR)

L20 ANSWER 3 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:439178 BIOSIS
DN PREV200000439178
TI NOS-2 mediates the protective anti-inflammatory and antifibrotic effects of the Th1-inducing **adjuvant**, IL-12, in a Th2 model of granulomatous disease.
AU Hesse, Matthias; Cheever, Allen W.; Jankovic, Dragana; Wynn, Thomas A. (1)
CS (1) Laboratory of Parasitic Diseases, NIH/NIAID, Bldg. 7, Room 318, Bethesda, MD, 20892 USA
SO American Journal of Pathology, (September, 2000) Vol. 157, No. 3, pp. 945-955. print.
ISSN: 0002-9440.
DT Article
LA English
SL English
AB Mice sensitized with Schistosoma mansoni eggs and IL-12 develop liver granulomas, on subsequent infection, which are esmaller and less fibrotic than those in nonsensitized mice. The protective response is accompanied by a shift in the type-2 cytokine profile to one dominated by type-1 cytokines. The deviated response is associated with marked increases in inducible **nitric oxide** synthase (NOS-2) activity.
Here, we demonstrate, by using NOS-2-deficient mice, that the anti-inflammatory and anti-fibrotic effects of the type-1 response are completely NOS-2-dependent. Strikingly, despite developing a polarized type-1 cytokine response that was similar in magnitude, the egg/IL-12-sensitized NOS-deficient mice developed granulomas 8 times larger than WT mice did. There was also no decrease in hepatic fibrosis in the sensitized mutant animals. Interferon-gamma-deficient mice failed to exhibit the exacerbated inflammatory response, despite displaying a marked deficiency in **nitric oxide** production. However, immune deviation was unsuccessful in the latter animals, which suggested that the increase in inflammation in NOS-deficient mice resulted from a polarized but **nitric oxide**-deficient type-1 response. These results reveal a beneficial role for NOS-2 in the regulation of inflammation and suggest that the ultimate success of Th2-to-Th1 immune deviation strategies will rely on the efficient activation of NOS-2 expression in downstream effector cells.
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Digestive System (Ingestion and Assimilation)
IT Parts, Structures, & Systems of Organisms
Th1 cells: blood and lymphatics, immune system; Th2 cells: blood and lymphatics, immune system
IT Diseases

liver fibrosis: digestive system disease
IT Chemicals & Biochemicals
IL-12 [interleukin-12]:
antifibrotic, antiinflammatory; **nitric oxide** synthase-2 [NOS-2]
IT Alternate Indexing
Liver Cirrhosis (MeSH)
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L20 ANSWER 4 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:382616 BIOSIS
DN PREV200000382616
TI Interleukin-12 (IL-12) enhancement of the cellular immune response against human immunodeficiency virus type 1 Env antigen in a DNA prime/vaccinia virus boost **vaccine** regimen is time and dose dependent: Suppressive effects of IL-12 boost are mediated by **nitric oxide**.
AU Gherardi, M. Magdalena; Ramirez, Juan C.; Esteban, Mariano (1)
CS (1) Centro Nacional Biotecnologia (CSIC), Campus Cantoblanco, 28049, Madrid Spain
SO Journal of Virology, (July, 2000) Vol. 74, No. 14, pp. 6278-6286. print. ISSN: 0022-538X.
DT Article
LA English
SL English
AB We previously demonstrated that codelivery of interleukin-12 (IL-12) with the human immunodeficiency virus type 1 (HIV-1) Env antigen from a recombinant vaccinia virus (rVV) can enhance the specific anti-Env cell-mediated immune (CMI) response. In the present study, we have investigated the effects of IL-12 in mice when it is expressed in a DNA prime/VV boost **vaccine** regimen. The delivery of IL-12 and Env product during priming with a DNA vector, followed by a booster with VV expressing the Env gene (rVVenv), was found to trigger the optimal CMI response compared with other immunization schedules studied. Significantly, if IL-12 is also delivered as a booster from the viral vector, an impairment of the effects of IL-12 was observed involving **nitric oxide** (NO), since it was overcome by specific inhibitors of inducible **NO synthase**. NO caused transient immunosuppression rather than impairment of viral replication. Moreover, at certain viral doses, coadministration of the NO inhibitor during the booster resulted in IL-12-mediated enhancement of the specific CD8+ T-cell response. In addition, the dose of the IL-12-encoding plasmid (pIL-12) and the route of administration of both vectors were relevant factors for optimal CMI responses. Maximal numbers of Env-specific CD8+ gamma interferon-secreting cells were obtained when 50 mug of pIL-12 was administered intramuscularly at priming, followed by an intravenous rVVenv boost. Our results demonstrate, in a murine model, critical parameters affecting the success of vaccination schedules based on a combination of DNA and VV vectors in conjunction with immunomodulators.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Pharmacology
IT Parts, Structures, & Systems of Organisms
CD8-positive T cell
IT Chemicals & Biochemicals
DNA prime/vaccina virus boost **vaccine**: **immunostimulant** - drug; Env: antigen; gamma interferon; immunomodulator; **interleukin-12** [**IL-12**]: boost, suppressive effects; **nitric oxide** ; **nitric oxide** synthase; pIL-12: plasmid
IT Miscellaneous Descriptors
CD8-positive T cell response; cellular immune response: enhancement
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae: Animal Viruses, Viruses, Microorganisms
ORGN Organism Name
human immunodeficiency virus type 1 [HIV-1] (Retroviridae): pathogen; mouse (Muridae): animal model, host
ORGN Organism Superterms
Animal Viruses; Animals; Chordates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates; Viruses
RN **10102-43-9** (**NITRIC OXIDE**)
125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:377239 BIOSIS
DN PREV200000377239
TI Direct stimulation of macrophages by IL-12 and IL-18: A bridge too far.
AU Golab, Jakub (1); Zagozdzon, Radoslaw; Stoklosal, Tomasz; Kaminski, Rafal;
Kozar, Katarzyna; Jakobisiak, Marek
CS (1) Department of Immunology, Institute of Biostructure, Medical University of Warsaw, ul. Chalubinskiego 5, 02-004, Warsaw Poland
SO Immunology Letters, (June 1, 2000) Vol. 72, No. 3, pp. 153-157. print. ISSN: 0165-2478.
DT Article
LA English
SL English
AB A novel pathway of autocrine macrophage activation based on a positive feedback loop involving interleukin (IL)-12, IL-18 and IFN-gamma has recently been suggested. However, the macrophage isolation technique employed to describe the above phenomenon does not allow obtaining a pure population of macrophages casting some doubt to its existence. In the present study, we show that even minor contamination with lymphoid cells of a pure population of macrophage-like cells (Raw 264.7) results in a marked production of **nitric oxide** after stimulation with both IL-12 and IL-18. Neither macrophage-like cells nor lymphoid cells were capable of secreting high amounts of **nitric oxide** after stimulation with IL-12 and/or IL-18. Based on these observations we hypothesize that proposed autocrine feedback loop of macrophage activation is rather paracrine in nature and involves direct stimulation of residual lymphoid cells to secrete IFN-gamma that is then capable of activating macrophages.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
lymphoid cell: blood and lymphatics, immune system; macrophage: blood

and lymphatics, direct **stimulation**, **immune** system
IT Chemicals & Biochemicals
interferon-gamma; **interleukin-12**; interleukin-18
IT Miscellaneous Descriptors
positive feedback loop
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Raw 264.7 cell line (Muridae): murine macrophage-like cell
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

L20 ANSWER 6 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:216872 BIOSIS
DN PREV200000216872
TI Tumor necrosis factor is required for the priming of peritoneal macrophages by trehalose dimycolate.
AU Oswald, Isabelle P.; Dozois, Charles M.; Fournout, Sylvie; Petit, Jean-Francois; Lemaire, Genevieve (1)
CS (1) UMR CNRS 8619, Universite Paris-Sud, Batiment 430, 91405, Orsay Cedex France
SO European Cytokine Network, (Dec., 1999) Vol. 10, No. 4, pp. 533-540. ISSN: 1148-5493.
DT Article
LA English
SL English
AB Trehalose dimycolate (TDM), a glycolipid present in the cell wall of Mycobacterium spp., is a powerful **immunostimulant**. We have developed an original model of macrophage activation where TDM is injected in vivo to prime peritoneal macrophages. These primed macrophages do not express inducible **NO synthase** (NOS II), however, they can be fully activated, i. e. induced to express NOS II and to develop a NOS II-dependent antiproliferative activity, following in vitro exposure to low concentrations of LPS. In a previous paper, we have shown that TDM-priming of mouse peritoneal macrophages is mediated by the sequential production of IL-12 and IFN-gamma. In the present paper, we investigated the role of TNF in the priming of macrophages by TDM. By semi-quantitative RT-PCR, we have shown that TDM injection induced transcription of TNF-alpha in peritoneal cells. TNF-mRNA levels peaked 5 hours after TDM injection and remained elevated for at least 32 hours. TNF expression was absolutely necessary for macrophage priming, as injection of an anti-TNF monoclonal antibody, 4 h before and 20 hours after TDM injection, prevented LPS-dependent activation of macrophages in vitro. This result was confirmed by the inability of TDM to prime macrophages from LT-alpha/TNF-alpha knockout (LT/TNFKO) mice. In addition, analysis of LT/TNFKO mice treated with TDM revealed that induction of the IL-12 transcript in their peritoneal cells and expression of a functional NADPH oxidase in macrophages are TNF-independent events.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
peritoneal macrophage: blood and lymphatics, immune system, primed
IT Chemicals & Biochemicals
IFN-gamma [interferon-gamma]; **IL-12** [

interleukin-12]: transcription; NADPH oxidase;
TNF-alpha [tumor necrosis factor-alpha]: expression, transcription; cytokine; **nitric oxide** synthase; trehalose dimycolate: **immunostimulant**, mycobacterial glycolipid
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Mycobacteriaceae: Mycobacteria, Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms
ORGN Organism Name
Mycobacterium spp. (Mycobacteriaceae); mouse (Muridae)
ORGN Organism Superterms
Animals; Bacteria; Chordates; Eubacteria; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 9032-22-8Q (NADPH OXIDASE)
37256-37-4Q (NADPH OXIDASE)
125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 7 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:216862 BIOSIS
DN PREV200000216862
TI **Immunostimulatory** DNA is a potent agonist of IL-12, IFNgamma and **nitric oxide** production by skin macrophages from Leishmania-susceptible mice.
AU von Stebut, E. (1); Udey, M. (1)
CS (1) Dermatology Branch, NCI, Bethesda, MD USA
SO Journal of Investigative Dermatology, (April, 2000) Vol. 114, No. 4, pp. 798.
Meeting Info.: 61st Annual Meeting of the Society for Investigative Dermatology. Chicago, Illinois, USA May 10-14, 2000
ISSN: 0022-202X.
DT Conference
LA English
SL English
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Integumentary
System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
skin macrophage: blood and lymphatics, immune system
IT Chemicals & Biochemicals
DNA; IFN-gamma [interferon-gamma]; **IL-12** [**interleukin-12**]; **nitric oxide**: production
IT Miscellaneous Descriptors
Meeting Abstract
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): BALB/C, Leishmania-susceptible
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **10102-43-9** (**NITRIC OXIDE**)

L20 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:49297 BIOSIS
DN PREV200000049297

TI Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit interleukin-12 transcription by regulating nuclear factor kappaB and Ets activation.
AU Delgado, Mario; Ganea, Doina (1)
CS (1) Dept. Biological Sciences, Rutgers Univ., 101 Warren St., Newark, NJ USA
SO Journal of Biological Chemistry, (Nov. 5, 1999) Vol. 274, No. 45, pp. 31930-31940.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB The vasoactive intestinal peptide (VIP) and the structurally related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) act as "macrophage-deactivating factors". We showed previously that VIP and PACAP inhibit the production of macrophage-derived tumor necrosis factor-alpha, interleukin (IL)-6, **nitric oxide**, and IL-12. This study examines the molecular mechanisms involved in the VIP/PACAP inhibition of IL-12 production. VIP and PACAP inhibit IL-12 (p40) gene expression by affecting both NF-kappaB binding and the composition of the Ets-2 binding complex. Both neuropeptides prevent the activation-induced nuclear translocation of the NF-kappaB components p65 and c-Rel by inhibiting the reduction in cytoplasmic IkappaBalpha. Moreover, VIP and PACAP inhibit the synthesis of the interferon responsive factor-1. The decrease in nuclear interferon responsive factor-1 and c-Rel results in alterations of the Ets-2-binding complex. Two transduction pathways, a cAMP-dependent and a cAMP-independent pathway, are involved in the inhibition of IL-12 gene expression and appear to differentially regulate the transcriptional factors involved. Because IL-12 participates in T cell activation and cytolytic T lymphocyte activity and promotes the differentiation of T helper cells into the Th1 subset, the understanding of the mechanisms that affect IL-12 production in normal and pathological conditions could contribute to immune response-based therapies or **vaccine** designs.
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Endocrine System (Chemical Coordination and Homeostasis)
IT Chemicals & Biochemicals
Ets protein: activation; **interleukin-12**; **interleukin-12** gene: transcription; nuclear factor kappa-B; pituitary adenylate cyclase-activating polypeptide; vasoactive intestinal peptide
RN 137061-48-4 (PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE)
37221-79-7 (VASOACTIVE INTESTINAL PEPTIDE)

L20 ANSWER 9 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:470750 BIOSIS
DN PREV199900470750
TI Pathology in schistosomiasis, mediated by a polarized TH2-type response, is prevented by a vaccination protocol employing RIL-12 as an **adjuvant** but protection is dependent on the induced expression of inducible **no synthase**.
AU Hesse, M. (1); Jankovic, D.; Cheever, A. W.; Modolell, M.; Wynn, T. A.

CS (1) Laboratory of Parasitic Diseases, National Institutes of Health, Bethesda, MD USA
SO American Journal of Tropical Medicine and Hygiene, (Sept., 1999) Vol. 61, No. 3 SUPPL., pp. 192-193.
Meeting Info.: 48th Annual Meeting of the American Society of Tropical Medicine and Hygiene Washington, D.C., USA November 28-December 2, 1999 American Society of Tropical Medicine and Hygiene
. ISSN: 0002-9637.
DT Conference
LA English
IT Major Concepts
Clinical Immunology (Human Medicine, Medical Sciences); Infection; Parasitology; Pharmacology
IT Diseases
schistosomiasis: parasitic disease
IT Chemicals & Biochemicals
inducible **NO synthase**: induced expression;
recombinant **IL-12**: **adjuvant**, **immunostimulant** - drug
IT Alternate Indexing
Schistosomiasis (MeSH)
IT Methods & Equipment
vaccination protocol: immunization method
IT Miscellaneous Descriptors
polarized TH2-type response; **vaccine** development; Meeting Abstract
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Trematoda:
Platyhelminthes, Helminthes, Invertebrata, Animalia
ORGN Organism Name
mouse (Muridae): iNOS-deficient; Schistosoma mansoni (Trematoda): parasite
ORGN Organism Superterms
Animals; Chordates; Helminths; Invertebrates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Platyhelminths; Rodents; Vertebrates
RN **125978-95-2** (**NO SYNTHASE**)

L20 ANSWER 10 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:456607 BIOSIS
DN PREV199900456607
TI Shedding of membrane-bound CD14 from lipopolysaccharide-stimulated macrophages by vasoactive intestinal peptide and pituitary adenylate cyclase activating polypeptide.
AU Delgado, Mario (1); Leceta, Javier; Abad, Catalina; Martinez, Carmen; Ganea, Doina; Gomariz, Rosa P.
CS (1) Departamento de Biologia Celular, Facultad de Biologia, Universidad Complutense, 28040, Madrid Spain
SO Journal of Neuroimmunology, (Sept. 1, 1999) Vol. 99, No. 1, pp. 61-71. ISSN: 0165-5728.
DT Article
LA English
SL English
AB Macrophage activation and deactivation play essential roles in the initiation and maintenance of a successful immune response. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase activating polypeptide (PACAP), two structurally related neuropeptides, act as

macrophage deactivating factors. We reported previously that VIP and PACAP
inhibit IL-6, IL-12, TNFalpha and NO production, and enhance IL-10 production, from lipopolysaccharide (LPS)-stimulated macrophages. In this study, we demonstrate that VIP and PACAP down-regulate the expression of CD14, the membrane-bound LPS receptor, by inducing its rapid shedding. The
soluble CD14 released by VIP and PACAP corresponds in size to the soluble CD14 released by PMA. Neither VIP/PACAP nor PMA, affect the steady-state levels of CD14 mRNA. The CD14 shedding induced by VIP/PACAP is mediated through the PAC1 specific receptors and the major transduction pathway involves the protein kinase C (PKC). The VIP/PACAP inhibition of TNFalpha andNO occurs through both CD14-dependent and -independent mechanisms, whereas the inhibition of IL-6 production appears to be strictly CD14-dependent. The shedding of CD14 by VIP and PACAP represents an important mechanism by which these neuropeptides limit the macrophage inflammatory response.

IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis)

IT Parts, Structures, & Systems of Organisms
macrophage: activation, blood and lymphatics, deactivation, lipopolysaccharide-**stimulated**, **immune** system

IT Chemicals & Biochemicals
lipopolysaccharide; phorbol 12-myristate 13-acetate; pituitary adenylate cyclase activating polypeptide: macrophage deactivating factor; protein kinase C; vasoactive intestinal peptide: macrophage deactivating factor; CD14 mRNA [CD14 messenger RNA]; CD14: membrane-bound, shedding; IL-10 [interleukin-10]: production; **IL-12** [**interleukin-12**]; IL-6 [interleukin-6]; NO [**nitric oxide**]: production; TNF alpha [tumor necrosis factor alpha]

IT Miscellaneous Descriptors
immune response; neuroimmunomodulation

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae): BALB/C

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN **10102-43-9** (**NITRIC OXIDE**)
16561-29-8 (PHORBOL 12-MYRISTATE 13-ACETATE)
137061-48-4 (PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE)
141436-78-4 (PROTEIN KINASE C)
37221-79-7 (VASOACTIVE INTESTINAL PEPTIDE)

L20 ANSWER 11 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:451219 BIOSIS
DN PREV199900451219
TI Synergistic effect of interferon-gamma and mannosylated liposome-incorporated doxorubicin in the therapy of experimental visceral leishmaniasis.
AU Kole, Labanyamoy; Das, Lopamudra; Das, Pijush K. (1)
CS (1) Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Calcutta, 700 032 India
SO Journal of Infectious Diseases, (Sept., 1999) Vol. 180, No. 3, pp.

811-820.
ISSN: 0022-1899.
DT Article
LA English
SL English
AB Active targeting of doxorubicin to macrophages was studied by incorporating it in mannosecoated liposomes by use of visceral leishmaniasis in BALB/c mice as the model macrophage disease. Mannosylated liposomal doxorubicin was more effective than liposomal doxorubicin or free doxorubicin. Because leishmaniasis is accompanied by **immunosuppression, immuno-stimulation** by interferon (IFN)-gamma was evaluated to act synergistically with mannosylated liposomal doxorubicin therapy. Combination chemotherapy with a suboptimal dose of IFN-gamma resulted in possibly complete elimination of spleen parasite burden. Analysis of mRNA levels of infected spleen cells suggested that targeted drug treatment together with IFN-gamma, in addition to greatly reducing parasite numbers, resulted in reduced levels of interleukin (IL)-4 but increased levels of IL-12 and inducible **nitric oxide** synthase. Such combination chemotherapy may provide a promising alternative for the cure of leishmaniasis, with a plausible conversion of antiparasitic T cell response from a Th2 to Th1 pattern indicative of long-term resistance.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology; Pharmacology
IT Parts, Structures, & Systems of Organisms
macrophage: blood and lymphatics, immune system; T cell: blood and lymphatics, immune system
IT Diseases
visceral leishmaniasis: experimental, model macrophage disease, parasitic disease
IT Chemicals & Biochemicals
doxorubicin: antiparasitic - drug, mannosylated liposome-incorporation;
inducible **nitric oxide** synthase; interferon-gamma: immunosuppressant - drug; **interleukin-12**; interleukin-4; mannosylated liposome; mRNA [messenger RNA]
IT Alternate Indexing
Leishmaniasis, Visceral (MeSH)
ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): BALB/c; Leishmania donovani (Flagellata): parasite
ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates
RN 23214-92-8 (DOXORUBICIN)
125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 12 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:445141 BIOSIS
DN PREV199900445141
TI Polarization of the immune response to the single immunodominant epitope of p38, a major Schistosoma mansoni egg antigen, generates Th1- or Th2-type cytokines and granulomas.

AU Chen, Yiguang; Boros, Dov L. (1)
CS (1) Department of Immunology and Microbiology, WSU School of Medicine, 540
E. Canfield Ave., Detroit, MI, 48201 USA
SO Infection and Immunity, (Sept., 1999) Vol. 67, No. 9, pp. 4570-4577.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB In schistosomiasis mansoni, helminth eggs secrete soluble egg antigens (SEA) that induce T-cell-mediated granulomatous tissue responses. The cloned 38-kDa peptide (p38) of SEA was shown to induce and elicit Th1-type responsiveness in H-2k mice. Subsequently, the immunodominant T-cell epitope (P4) of p38 was shown to elicit pulmonary granuloma formation and Th1-type cytokine production in sensitized or infected mice. Here, we report that the immune response to p38 or P4 can be polarized to a Th1 or Th2 profile when the peptides are presented intraperitoneally in soluble recombinant interleukin-12 (IL-12) or alum **adjuvant**, respectively. The Th1 or Th2 profile was verified by cytokine secretion, enzyme-linked spot assay, and antibody isotype characterization. Importantly, the polarized immune response generated two types of pulmonary granulomas around injected P4-coated beads. The type 1 granulomas were smaller and contained mononuclear cells and occasional thin strands of deposited collagen. In contrast, the type 2 lesions were larger and contained mononuclear cells, large numbers of eosinophils, and several thick bands of deposited collagen. By reverse transcription-PCR cytokine, message in the type 1 granuloma-bearing lungs was found for gamma interferon, tumor necrosis factor alpha, and inducible **nitric oxide** synthase but not for IL-4 or IL-5. Conversely, lungs with type 2 granulomas had message only for IL-4 and IL-5. These results show that in the proper cytokine environment, the response to a strong Th1 inducer peptide can be deviated to a Th2 profile.
IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis); Parasitology
IT Parts, Structures, & Systems of Organisms
T cell: blood and lymphatics, immune system
IT Diseases
pulmonary granuloma: formation, respiratory system disease
IT Chemicals & Biochemicals
gamma interferon; inducible **nitric oxide** synthase; interleukin-4; interleukin-5; p38: immune response, immunodominant epitope, polarization, major Schistosoma mansoni egg antigen; soluble egg antigen: secretion; soluble recombinant **interleukin-12**; tumor necrosis factor alpha
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Trematoda:
Platyhelminthes, Helminthes, Invertebrata, Animalia
ORGN Organism Name
mouse (Muridae); Schistosoma mansoni (Trematoda): parasite
ORGN Organism Superterms
Animals; Chordates; Helminths; Invertebrates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Platyhelminths; Rodents; Vertebrates
RN **125978-95-2** (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 13 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:136233 BIOSIS
DN PREV199900136233
TI Ex vivo effects of lactobacilli, streptococci, and bifidobacteria ingestion on cytokine and **nitric oxide** production in a murine model.
AU Tejada-Simon, Maria Victoria; Ustunol, Zeynep; Pestka, James J. (1)
CS (1) Dep. Food Sci. and Human Nutrition, Michigan State Univ., East Lansing, MI 48824-1224 USA
SO Journal of Food Protection, (Feb., 1999) Vol. 62, No. 2, pp. 162-169. ISSN: 0362-028X.
DT Article
LA English
AB Increasing numbers of functional foods and pharmaceutical preparations are being promoted with health claims based on the potential probiotic characteristics of lactic acid bacteria and on their capacity for **stimulating** the host **immune** system. However, the specific immune effects of oral administration of these microbes still remains undefined. In this study, we tested the hypothesis that production of immunologic mediators by leukocytes in mice is affected by orally administered lactic acid bacteria. The specific objectives of this study were to evaluate the effects of exposure to eight different lactic acid bacteria in mice on ex vivo cytokine and **nitric oxide** production in leukocyte cultures. Mice were gavaged with 1 X 109 viable bacteria and peritoneal, Peyer's patch and splenic leukocytes were isolated 8 h later. These were cultured for 2 or 5 days in the presence or absence of mitogens and then interleukin (IL)-6, IL-12, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, and **nitric oxide** production was measured. The results revealed that Lactobacillus acidophilus and L. casei potentiated IL-6 and IL-12 production by peritoneal cells whereas L. acidophilus upregulated IFN-gamma and **nitric oxide**. In contrast, L. helveticus, L. gasseri, L. reuteri, and Bifidobacterium attenuated the production of IL-6, IFN-gamma, and **nitric oxide** by peritoneal cells. TNF-alpha was not detectable in peritoneal cultures. None of the bacteria altered ex vivo production of cytokines or **nitric oxide** by Peyer's patch or spleen cell cultures. Taken together, the results suggest that prior oral exposure to lactic acid bacteria could differentially potentiate or attenuate subsequent cytokine and **nitric oxide** production by peritoneal cells.
IT Major Concepts
Foods; Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
peritoneal leukocytes: blood and lymphatics, immune system; splenic leukocytes: blood and lymphatics, immune system; Peyer's patch leukocytes: blood and lymphatics, immune system
IT Chemicals & Biochemicals
interferon-gamma: production; **interleukin-12**: production; interleukin-6: production; **nitric oxide** : production; tumor necrosis factor-alpha: production
IT Miscellaneous Descriptors
functional foods: health food

ORGN Super Taxa
Gram-Positive Cocci: Eubacteria, Bacteria, Microorganisms; Irregular Nonsporing Gram-Positive Rods: Actinomycetes and Related Organisms, Eubacteria, Bacteria, Microorganisms; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Regular Nonsporing Gram-Positive Rods: Eubacteria, Bacteria, Microorganisms
ORGN Organism Name
mouse (Muridae): animal model; Bifidobacterium (Irregular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus acidophilus (Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus bulgaricus (Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus casei (Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus gasseri (Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus helveticus (Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Lactobacillus reuteri (Regular Nonsporing Gram-Positive Rods): oral ingestion, probiotic; Streptococcus thermophilus (Gram-Positive Cocci): oral ingestion, probiotic
ORGN Organism Superterms
Animals; Bacteria; Chordates; Eubacteria; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **10102-43-9 (NITRIC OXIDE)**

9/98
1/98

L20 ANSWER 14 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:13829 BIOSIS
DN PREV199900013829
TI Immune suppression by recombinant interleukin (rIL)-12 involves interferon
gamma induction of **nitric oxide** synthase 2 (iNOS)
activity: Inhibitors of NO generation reveal the extent of rIL-12 **vaccine adjuvant** effect.
AU Koblish, Holly Kurzawa; Hunter, Christopher A.; Wysocka, Maria; Trinchieri, Giorgio; Lee, William M. F. (1)
CS (1) 663 Clin. Res. Build., 415 Curie Blvd., Univ. Pennsylvania, Philadelphia, PA 19104-6140 USA
SO Journal of Experimental Medicine, (Nov. 2, 1998) Vol. 188, No. 9, pp. 1603-1610.
ISSN: 0022-1007.
DT Article
LA English
AB Recombinant interleukin 12 (IL-12) can profoundly suppress cellular immune
responses in mice. To define the underlying mechanism, recombinant murine (rm)IL-12 was given to C57BL/6 mice undergoing alloimmunization and found to transiently but profoundly suppress in vivo and in vitro allogeneic responses and in vitro splenocyte mitogenic responses. Use of neutralizing
antibodies and genetically deficient mice showed that IFN-gamma (but not TNF-alpha) mediated rmIL-12-induced immune suppression. Splenocyte fractionation studies revealed that adherent cells from rmIL-12-treated mice suppressed the mitogenic response of normal nonadherent cells to concanavalin A and IL-2. Addition of an inhibitor of **nitric oxide** synthase (NOS) restored mitogenic responses, and inducible (i)NOS-/- mice were not immnosuppressed by rmIL-12. These results support the view that suppression of T cell responses is due to NO produced by macrophages responding to the high levels of IFN-gamma induced by rmIL-12.

When a NOS inhibitor was given with rmIL-12 during vaccination of A/J mice with irradiated SCK tumor cells, immunosuppression was averted and the extent of rmIL-12's ability to enhance induction of protective antitumor immunity was revealed. This demonstrates that rmIL-12 is an effective **vaccine adjuvant** whose efficacy may be masked by its transient immunosuppressive effect.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Pharmacology

IT Chemicals & Biochemicals
interferon gamma; **nitric oxide** synthase 2: activity, induction; **nitric oxide**: synthesis; recombinant **interleukin-12**: immunosuppressive agent, **vaccine**

RN **125978-95-2** (**NITRIC OXIDE** SYNTHASE)
10102-43-9 (**NITRIC OXIDE**)

L20 ANSWER 15 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:389812 BIOSIS
DN PREV199800389812
TI Effects of interleukin-12 in vitro on pancreatic islets isolated from normal rodents and from non-obese diabetic mice.
AU Sternesjo, J. (1); Sandler, S.
CS (1) Dep. Med. Cell Biol., Uppsala Univ. Biomedicum, P.O. Box 571, S-751 23 Uppsala Sweden
SO Journal of Endocrinology, (July, 1998) Vol. 158, No. 1, pp. 69-75. ISSN: 0022-0795.
DT Article
LA English
AB Administration of the T-helper 1 (Th1) cell promoting cytokine interleukin-12 (IL-12) accelerates the development of autoimmune diabetes in non-obese diabetic (NOD) mice. In this study we examined the effects of IL-12 on isolated islets from NMRI (Naval Medical Research Institute-established) mice, Sprague-Dawley (S-D) rats and NOD mice. NMRI and S-D islets were cultured in medium RPMI 1640 + 10% fetal calf serum and exposed for 48 h to recombinant mouse IL-12 (0, 0.1, 1 and 10 ng/ml). Islet glucose metabolism, as measured by glucose oxidation rate, was suppressed by about 25% in NMRI islets exposed to 10 ng/ml IL-12. In rat islets 0.1 ng/ml IL-12 induced a 20% decrease in glucose oxidation rate. Islets cultured with 10 ng/ml IL-12 showed a decrease in medium insulin accumulation both in mouse and rat. Glucose-stimulated insulin release was lowered in rat islets exposed to 10 ng/ml IL- 12, but not affected in NMRI islets. In NMRI islets IL-12 did not influence **nitric oxide** production as measured by nitrite formation. In rat islets IL-12 induced a decrease in nitrite formation compared with control islets. Islets were isolated from female NOD mice (age 5, 12, 20 and 26 weeks) and examined either immediately or cultured for 7 days with 10 ng/ml IL-12 alone or in combination with 4 ng/ml of the T-cell stimulating cytokine interleukin-2 (IL-2). In the age groups >5 weeks of age the glucose-stimulated insulin release was lower in freshly isolated compared with cultured control islets. IL-2+IL-12 addition induced a small decrease

in glucose-stimulated insulin release in islets from 12-week-old animals. With increasing age the DNA content in freshly isolated islets increased due to immune cell infiltration. The DNA content in cultured islets was decreased by 40-60% compared with freshly isolated islets in the age groups over 5 weeks. Islet insulin content was similar in both freshly isolated and cultured islets. None of the cytokines, either alone or in combination, affected islet DNA or insulin content. We conclude that IL-12 has minor suppressive effects in vitro on normal rodent islets. It is likely that the reported accelerated diabetes development of IL-12 administration to NOD mice in vivo is not mediated by a direct toxic effect to the islets. The suppressed insulin release in NOD mouse islets treated with IL-2+IL-12 suggests, however, that the accelerating effect might partly be attributed to **stimulation** of **immune** cells present in the insulitic lesion.

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
pancreatic islets: endocrine system; T-helper lymphocyte: immune system
IT Diseases
diabetes: accelerated, endocrine disease/pancreas, metabolic disease
IT Chemicals & Biochemicals
insulin: release; **interleukin-12**; interleukin-2; **nitric oxide**; DNA
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Rodentia: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): NMRI, NOD; rat (Muridae): Sprague-Dawley; rodent (Rodentia)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 9004-10-8 (INSULIN)
10102-43-9 (NITRIC OXIDE)

L20 ANSWER 16 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:216334 BIOSIS
DN PREV199800216334
TI The role of Il-12 in experimental Trypanosoma cruzi infection.
AU Silva, J. S. (1); Aliberti, J. C. S.; Martins, G. A.; Souza, M. A.; Souto, J. T.; Padua, M. A.
CS (1) Departamento de Parasitologia, Microbiologia e Imunologia, FMRP, USP, Av. Bandeirantes 3900, 14049-9000 Ribeirao Preto, SP Brazil
SO Brazilian Journal of Medical and Biological Research, (Jan., 1998) Vol. 31, No. 1, pp. 111-115.
ISSN: 0100-879X.
DT Article
LA English
AB Host resistance to Trypanosoma cruzi infection is dependent on both natural and acquired immune responses. During the early acute phase of infection in mice, natural killer (NK) cell-derived IFN-gamma is involved in controlling intracellular parasite replication, mainly through the

induction of **nitric oxide** biosynthesis by activated macrophages. We have shown that IL-12, a powerful inducer of IFN-gamma production by NK cells, is synthesized soon after trypomastigote-macrophage interaction. The role of IL-12 in the control of T. cruzi infection in vivo was determined by treating infected mice with anti-IL-12 monoclonal antibody (mAb) and analyzing both parasitemia and mortality during the acute phase of infection. The anti-IL-12 mAb-treated mice had higher levels of parasitemia and mortality compared to control mice. Also, treatment of infected mice with mAb specific for IFN-gamma or TNF-alpha inhibited the protective effect of exogenous IL-12. On the other hand, TGF-B and IL-10 produced by infected macrophages inhibited the induction and effects of IL-12. Therefore, while IL-12, TNF-alpha and IFN-gamma correlate with resistance to T. cruzi infection, TGF-Band IL-10 promote susceptibility. These results provide support for a role of innate immunity in the control of T. cruzi infection. In addition to its protective role, IL-12 may also be involved in the modulation of T. cruzi-induced myocarditis, since treatment of infected mice with IL-12 or anti-IL-12 mAb leads to an enhanced or decreased inflammatory infiltrate in the heart, respectively. Understanding the role of the cytokines produced during the acute phase of T. cruzi infection and their involvement in protection and pathogenesis would be essential to devise new **vaccines** or therapies.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Parts, Structures, & Systems of Organisms
macrophage: blood and lymphatics, immune system; natural killer cell: blood and lymphatics, immune system

IT Diseases
Trypanosoma cruzi infection: parasitic disease

IT Chemicals & Biochemicals
cytokines; **Il-12** [**interleukin-12**]: cytokine

IT Miscellaneous Descriptors
experimental infections; pathogenesis

ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae); Trypanosoma-cruzi (Flagellata): parasite

ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates

L20 ANSWER 17 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:170056 BIOSIS
DN PREV199800170056
TI Control of coccidiosis: Lessons from other sporozoa.
AU Cox, F. E. G. (1)
CS (1) Div. Life Sci., Kings Coll. London, Campden Hill Road, London W8 7AH UK
SO International Journal for Parasitology, (Jan., 1998) Vol. 28, No. 1, pp. 165-179.
ISSN: 0020-7519.
DT General Review
LA English

AB Coccidiosis is the most important parasitic infection in poultry worldwide
and also causes problems in cattle, sheep and goats. Control is largely limited to good husbandry and prophylactic chemotherapy using a range of drugs against which resistance is rapidly acquired. Attempts at vaccination using conventional **vaccines** have been disappointing and there is now a need for a new approach. Research into the immunology of coccidiosis has lagged behind that of other sporozoans and there are useful lessons that might be learned from studies on toxoplasmosis, cryptosporidiosis, theileriosis and malaria. In these infections the emphasis has turned to the cytokine network that drives the response towards protection. Central to these studies are the roles of interferon-gamma, interleukin-12 and activated macrophages with the involvement of **nitric oxide** in parasite killing.
Cytotoxic T cells have also increasingly been implicated. Research has shown that different immune responses can be elicited by manipulating the
cytokine system and these new concepts can be applied to the design of peptide or recombinant **vaccines**, and the possibilities of developing such **vaccines** against coccidiosis will be discussed.

IT Major Concepts
Parasitology

IT Parts, Structures, & Systems of Organisms
activated macrophages: blood and lymphatics, immune system; cytotoxic T
cells: blood and lymphatics, immune system

IT Diseases
coccidiosis: parasitic disease; cryptosporidiosis: digestive system disease, parasitic disease; theileriosis: parasitic disease; toxoplasmosis: parasitic disease

IT Chemicals & Biochemicals
interferon-gamma; **interleukin-12**

IT Methods & Equipment
vaccination: prophylactic method

IT Miscellaneous Descriptors
disease control strategies; immunology; prophylactic chemotherapy

L20 ANSWER 18 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:125261 BIOSIS
DN PREV199800125261
TI The debate over the effector function of eosinophils in helminth infection: New evidence from studies on the regulation of **vaccine** immunity by IL-12.
AU Wynn, Thomas A. (1)
CS (1) Immunobiol. Section, Lab. Parasitic Diseases, Natl. Inst. Allergy Infectious Diseases, Natl. Institutes Health, Bethesda, MD 20892 USA
SO Memorias do Instituto Oswaldo Cruz, (Dec. 30, 1997 (1998)) Vol. 92, No. SUPPL. 2, pp. 105-108.
ISSN: 0074-0276.
DT Article
LA English
AB The production of Th1-type cytokines is associated with strong cell-mediated immunity while Th2-type cytokines are typically involved in the generation of humoral immune responses. In mice vaccinated a single time (1X) with attenuated cercariae of Schistosoma mansoni, the immunity induced is highly dependent on CD4+ T cells and IFN-gamma. In contrast, mice vaccinated multiple times (3X) have decreased IFN-gamma expression,

develop a more dominant Th2-type cytokine response as well as protective antibodies which can passively transfer immunity to naive recipients. Previously, we demonstrated the ability of IL-12, a potent IFN-gamma-inducing cytokine to enhance (IX) schistosome cell-mediated immunity when administered during the period of immunization. More recently, we asked what effects IL-12 would have on the development humoral-based immunity. While multiply-immunized/saline-treated mice demonstrated a 70-80% reduction in parasite burden, 3X/IL-12-vaccinated animals displayed an even more striking >90% reduction in challenge infection, with many mice in the later group demonstrating complete protection. Analysis of pulmonary cytokine mRNA responses demonstrated that control challenged mice elicited a dominant Th2-type response, 3X/saline-vaccinated produced a mixed Th1/Th2-type cytokine response, while 3X/IL-12-immunized animals displayed a dominant Th1-type response. The IL-12-treated group also showed a marked reduction in total serum IgE and tissue eosinophilia while SWAP-specific IgG2a and IgG2b Abs were elevated. Interestingly, animals vaccinated with IL-12 also showed a highly significant increase in total Ig titers specific for IrV-5, a known protective antigen. More importantly, 3X/IL-12 serum alone, when transferred to naive mice reduced worm burdens by over 60% while 3X/saline serum transferred significantly less protection. Nevertheless, animals vaccinated in the presence of IL-12 also develop macrophages with enhanced **nitric oxide** dependent killing activity against the parasites. Together these observations suggest that IL-12, initially described as an **adjuvant** for cell-mediated immunity, may also be used as an **adjuvant** for promoting both humoral and cell-mediated protective responses.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology
IT Parts, Structures, & Systems of Organisms
eosinophil: blood and lymphatics, immune system; CD4 positive T cell: immune system
IT Chemicals & Biochemicals
immunoglobulin E; immunoglobulin G2a; immunoglobulin G2b; interferon-gamma; **interleukin-12**
IT Miscellaneous Descriptors
humoral immune response; **vaccine** immunity
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Trematoda: Platyhelminthes, Helminthes, Invertebrata, Animalia
ORGN Organism Name
mouse (Muridae): parasite host; Schistosoma-mansoni (Trematoda): parasite
ORGN Organism Superterms
Animals; Chordates; Helminths; Invertebrates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Platyhelminths; Rodents; Vertebrates

L20 ANSWER 19 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:6581 BIOSIS
DN PREV199800006581
TI Cytokines and **nitric oxide** as effector molecules against parasitic infections.
AU Liew, Foo Y. (1); Wei, Xiao-Qing; Proudfoot, Lorna

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L2          1809 S NITRIC OXIDE
L3            85 S NO SYNTHASE
L4             5 S L1 AND (L2 OR L3)
L5            21 S L NAME OR L NMMA
L6            66 S ?METHYL ARGININE OR  ?ARGININE (W) (METHYLESTER OR METHYL
EST
L7            77 S L5 OR L6
L8             1 S L1 AND L7
L9             5 S L8 OR L4

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L9   ANSWER 1 OF 5  WPIDS COPYRIGHT 2001   DERWENT INFORMATION LTD
AN   2001-007219 [01]   WPIDS
DNC  C2001-001834
TI   Protecting pancreatic islet beta-cells from immune system-mediated
     toxicity, used to prevent Type I diabetes, by transducing beta-cells with
     genetically modified adeno-associated virus vectors.
DC   B04 D16
IN   BLEICH, D; NADLER, J L; PRASAD, K
PA   (CITY) CITY OF HOPE
CYC  91
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        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
            OA PT SD SE SL SZ TZ UG ZW
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CS (1) Dep. Immunol., Univ. Glasgow, Glasgow G11 6NT UK
SO Philosophical Transactions of the Royal Society of London B Biological Sciences, (Sept. 29, 1997) Vol. 352, No. 1359, pp. 1311-1315. ISSN: 0962-8436.
DT Article
LA English
AB **Nitric oxide** (NO) derived from L-arginine by the catalytic action of inducible **NO synthase** (iNOS) plays an important role in killing parasites. Many cell types express high levels of iNOS when activated by a number of **immunological stimuli** which include interferon-gamma (IFN-gamma), tumour necrosis factor alpha, and lipopolysaccharide. IFN-gamma is typically produced by the Th1 subset of CD4+ T cells, whose differentiation depends on interleukin-12 (IL-12) produced by macrophages. Mice with a disrupted iNOS gene were highly susceptible to Leishmania major infection compared with similarly infected control wild-type mice. The mutant mice developed significantly higher levels of TH1-cell response compared with the control mice, suggesting that NO is likely to be the effector molecule in the immunological control of this and other intracellular parasitic infections. To ensure their survival, the Leishmania parasites have evolved effective means to inhibit NO synthesis. The highly conserved major surface glycolipids, glycoinositol-phospholipids and lipophosphoglycan (LPG), of Leishmania are potent inhibitors of NO synthesis. Furthermore, LPG can also inhibit IL-12 synthesis, thereby indirectly blocking the induction of iNOS. The evolutionary and therapeutic implications of these findings are discussed.
IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology
IT Chemicals & Biochemicals
cytokines; glycoinositol-phospholipids; interferon-gamma; **interleukin-12** [**IL-12**]; iNOS gene [inducible **nitric oxide** synthase gene]; lipophosphoglycan; **nitric oxide**; surface glycolipids; tumor necrosis factor-alpha
ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae): parasite host; Leishmania (Flagellata): parasite; Leishmania-major (Flagellata): parasite
ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates
RN **10102-43-9** (**NITRIC OXIDE**)
125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 20 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:392518 BIOSIS
DN PREV199799691721
TI Lipopolysaccharide and monophosphoryl lipid A differentially regulate interleukin-12, gamma interferon, and interleukin-10 mRNA production in murine macrophages.
AU Salkowski, Cindy A.; Detore, Gregory R.; Vogel, Stefanie N. (1)
CS (1) Dep. Microbiol. Immunol., Uniformed Services Univ. Health Sci., 4301 Jones Bridge Rd., Bethesda, MD 20814 USA
SO Infection and Immunity, (1997) Vol. 65, No. 8, pp. 3239-3247.

ISSN: 0019-9567.
DT Article
LA English
AB Monophosphoryl lipid A (MPL) is a nontoxic derivative of the lipid A region of lipopolysaccharide (LPS) that is being developed as both an **adjuvant** and prophylactic drug for septic shock. We compared the ability of LPS and MPL to induce interleukin-10 (IL-10), IL-12 p35, IL-12 p40, gamma interferon (IFN-gamma), glucocorticoid receptor (GR), IL-1 receptor antagonist (IL-Ira), and inducible **nitric oxide** synthase mRNA expression in murine peritoneal macrophages. These genes were chosen for their ability to positively or negatively regulate the host immune response and thus for their potential involvement in MPL-induced adjuvanticity or in its ability to protect against sepsis. LPS was a more potent inducer of IL-12 p35, IL-12 p40, and IFN-gamma mRNA, as well as of IL-12 protein, than MPL. In contrast, MPL induced higher levels of IL-10 mRNA than did LPS from 1 to 1,000 ng/ml. In general, MPL was not a more potent inducer of negative regulatory genes, since MPL and LPS induced similar levels of GR and IL-1ra mRNA. Addition of anti-IL-10 antibody to cultures increased the induction of MPL-induced IL-12 p35, IL-12 p40, and IFN-gamma mRNA, suggesting that the enhanced production of IL-10 by MPL-stimulated macrophages contributes to decreased production of mRNA for IL-12 (p35 and p4-) and IFN-gamma. Conversely, the addition of exogenous IL-10 to LPS-treated macrophages reduced the mRNA expression of these cytokine genes. These studies suggest that enhanced production of IL-10 by MPL-stimulated macrophages may contribute to the reduced toxicity of MPL through its negative action on induction of cytokines shown to enhance endotoxicity.
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Infection; Membranes (Cell Biology); Toxicology
IT Chemicals & Biochemicals
LIPID A; **NITRIC OXIDE** SYNTHASE
IT Miscellaneous Descriptors
BACTERIAL DISEASE; BLOOD AND LYMPHATICS; ENDOTOXICITY; GAMMA-INTERFERON; GLUCOCORTICOID RECEPTOR; HOST IMMUNE RESPONSE; IMMUNE SYSTEM; INDUCIBLE **NITRIC OXIDE** SYNTHASE; INTERLEUKIN-1 RECEPTOR ANTAGONIST; INTERLEUKIN-10; **INTERLEUKIN -12** P35; **INTERLEUKIN-12** P40; LIPOPOLYSACCHARIDE; MESSENGER RNA; MONOPHOSPHORYL LIPID A; MRNA; PERITONEAL MACROPHAGES; SEPTIC SHOCK
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 95991-05-2 (LIPID A)

125978-95-2 (**NITRIC OXIDE** SYNTHASE)

L20 ANSWER 21 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:204629 BIOSIS
DN PREV199799503832
TI Interleukin-12 synthesis is a required step in trehalose dimycolate-induced activation of mouse peritoneal macrophages.
AU Oswald, Isabelle P.; Dozois, Charles M.; Petit, Jean-Francois; Lemaire, Genevieve (1)
CS (1) URA CNRS 1116, Batiment 430, Univ. Paris Sud, 91405 Orsay Cedex France
SO Infection and Immunity, (1997) Vol. 65, No. 4, pp. 1364-1369. ISSN: 0019-9567.
DT Article
LA English
AB Trehalose dimycolate (TDM), a glycolipid present in the cell wall of Mycobacterium spp., is a powerful **immunostimulant**. TDM primes murine macrophages (M-vphi) to produce **nitric oxide** (NO) and to develop antitumoral activity upon activation with low doses of lipopolysaccharide (LPS). In this study, we investigated the ability of TDM to induce interleukin 12 (IL-12) and the role of this cytokine in TDM-induced activation of murine M-vphi. RNA isolated from peritoneal exudate cells (PEC) collected at different times after TDM injection was used to determine IL-12 (p35 and p40 subunits) and gamma interferon (IFN-gamma) mRNA levels by semiquantitative reverse transcriptase-PCR. Constitutive expression of IL-12p35 was observed in PEC from untreated as well as from TDM-injected mice. In contrast, expression of the IL-12p40 subunit was almost undetectable in control PEC but was dramatically upregulated in PEC from TDM-injected mice. IL-12p40 expression peaked at 8 h and subsided to baseline levels at 39 h postinjection. TDM was also able to induce IFN-gamma expression; however, kinetics of induction of IFN-gamma was different from that of IL-12p40. Maximal levels of IFN-gamma mRNA were reached by 24 h and did not return to baseline by 4 days. In addition, pretreatment of mice with neutralizing monoclonal antibodies directed against IL-12 (C15.6.7 and C15.1.2) blocked IFN-gamma mRNA induction in PEC from TDM-treated mice. We further determined if the induction of IL-12 and/or IFN-gamma contributes to the in vivo priming effect of TDM on peritoneal M-vphi. TDM-injected mice were treated in vivo with anti-IL-12 or anti-IFN-gamma (XMG.1.6) monoclonal antibodies. TDM-primed M-vphi were then activated in vitro with LPS and tested for their ability to produce NO and to develop cytostatic activity toward cocultivated L1210 tumor cells. Priming of M-vphi by TDM was completely blocked by in vivo neutralization of either IL-12 or IFN-gamma as demonstrated by an absence of tumoricidal activity and NO production by TDM-elicited M-vphi in the presence of LPS. Taken together our results show that TDM, a defined molecule from M. tuberculosis, induces in vivo production of IL-12. Moreover, synthesis of IL-12 mediates TDM priming of mouse peritoneal M-vphi through IFN-gamma induction.
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination

and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Metabolism
IT Chemicals & Biochemicals
TREHALOSE
IT Miscellaneous Descriptors
BLOOD AND LYMPHATICS; ENDOCRINE SYSTEM; IMMUNE SYSTEM; INTERFERON-GAMMA; **INTERLEUKIN-12**; MACROPHAGE; TREHALOSE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 99-20-7 (TREHALOSE)

L20 ANSWER 22 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:24081 BIOSIS
DN PREV199799323284
TI Toxoplasma gondii: Evidence of interleukin-12-dependent and -independent pathways of interferon-gamma production induced by an attenuated parasite strain.
AU Scharton-Kersten, Tanya (1); Caspar, Patricia (1); Sher, Alan (1); Denkers, Eric Y.
CS (1) Immunobiol. Sect., Lab. Parasitic Dis., Natl. Inst. Allergy Infect. Dis., Bethesda, MD 20892 USA
SO Experimental Parasitology, (1996) Vol. 84, No. 2, pp. 102-114. ISSN: 0014-4894.
DT Article
LA English
AB Immunity in mice infected with Toxoplasma gondii is dependent upon the ability to generate protective levels of the cytokine IFN-gamma. In this report, we present evidence that the attenuated **vaccine** strain, ts-4, induces the latter cytokine by both IL-12-dependent and -independent pathways. In contrast, strain ME49 appears to induce IFN-gamma wholly in dependence upon IL-12. Thus, 88% of wild-type C57BL/6 mice treated with anti-IL-12 mAb survive ts-4 infection, unlike similarly treated ME49-infected animals. Moreover, while anti-IL-12 treatment reduced early IFN-gamma and **nitric oxide** production to background levels in ts-4-infected scid animals, the same treatment in infected C57BL/6 mice had no effect on production of the latter mediators. In addition, we found that anti-IL-12 treatment induces 100% mortality in CD4+-deficient MHC class II knockout mice infected with ts-4. Finally, production of **nitric oxide** (a molecule implicated in parasite control) was abrogated in ts-4-infected scid mice following depletion of IFN-gamma producing NK cells. Together, our results suggest that ts-4 induces IL-12-dependent and -independent IFN-gamma production in normal mice, but ME49 induces the latter cytokine only in dependence upon IL-12. Our data, furthermore, implicate involvement of T cells in the IL-12-independent component of the IFN-gamma response.
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Genetics; Immune System (Chemical Coordination and Homeostasis); Parasitology

IT Chemicals & Biochemicals
NITRIC OXIDE
IT Miscellaneous Descriptors
BLOOD AND LYMPHATICS; C57BL/6 MOUSE; C57BL/6 SCID MOUSE; IMMUNE SYSTEM;
INTERFERON-GAMMA; **INTERLEUKIN-12**; **NITRIC OXIDE**; PARASITE; PARASITE HOST; PARASITOLOGY; PRODUCTION;
SEVERE COMBINED IMMUNODEFICIENCY; STRAIN-ME49; STRAIN-TS-4; T CELL
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Sporozoa: Invertebrata, Protozoa, Animalia
ORGN Organism Name
Muridae (Muridae); Toxoplasma gondii (Sporozoa)
ORGN Organism Superterms
animals; chordates; invertebrates; mammals; microorganisms; nonhuman mammals; nonhuman vertebrates; protozoans; rodents; vertebrates
RN **10102-43-9** (**NITRIC OXIDE**)

L20 ANSWER 23 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:299361 BIOSIS
DN PREV199598313661
TI IL-12 enhances **vaccine**-induced immunity to Schistosoma mansoni in mice and decreases T helper 2 cytokine expression, IgE production and tissue eosinophilia.
AU Wynn, Thomas A. (1); Jankovic, Dragana; Hieny, Sara; Cheever, Allen W.; Sher, Alan
CS (1) 9000 Rockville Pike, Natl. Inst. Health, Build. 4/126, Bethesda, MD 20892 USA
SO Journal of Immunology, (1995) Vol. 154, No. 9, pp. 4701-4709. ISSN: 0022-1767.
DT Article
LA English
AB Vaccination of mice with radiation-attenuated cercariae of Schistosoma mansoni results in a highly significant but partial protection against challenge infection. This immunity is dependent on CD4+ T cells, and because of its suppression by anti-IFN-gamma, appears to be caused by a Th1 response. Nevertheless, both Th1 and Th2 lymphokines are expressed in vaccinated and challenged mice, and we hypothesized that the expression of the latter group of down-regulatory cytokines may be responsible for the failure to obtain complete protection. Because IL-12 is a key cytokine that suppresses Th2-like responses, we asked whether IL-12 could increase **vaccine**-induced immunity to S. mansoni. Indeed, administration of IL-12 significantly reduced worm burdens following a challenge infection. IL-12-treated animals displayed a marked increase in pulmonary IFN-gamma and IL-12 p40 mRNA expression, while levels of IL-4, IL-5, and IL-13 were suppressed significantly during the period of vaccination. A marked decrease in serum IgE and tissue eosinophilia, two responses regulated by Th2 cytokines, was also observed. Surprisingly, IL-12-treated/vaccinated mice failed to demonstrate a significant increase in IFN-gamma, TNF-alpha, or **nitric oxide** synthase mRNA at the time of challenge infection when compared with vaccinated controls, but did, however, display significantly suppressed Th2 cytokine mRNA production. Together, these data demonstrate that exogenous IL-12 regulates Th1/Th2 responses during immunization with irradiated cercariae, and suggest that this cytokine may be used to increase **vaccine**-induced immunity to S.

mansoni.
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Endocrine System (Chemical Coordination
and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Membranes (Cell Biology); Parasitology; Pharmacology; Physiology
IT Miscellaneous Descriptors
IMMUNOGLOBULIN E; **INTERLEUKIN-12**
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Trematoda:
Platyhelminthes, Helminthes, Invertebrata, Animalia
ORGN Organism Name
mouse (Muridae); Schistosoma mansoni (Trematoda)
ORGN Organism Superterms
animals; chordates; helminths; invertebrates; mammals; nonhuman mammals; nonhuman vertebrates; platyhelminths; rodents; vertebrates

L20 ANSWER 24 OF 24 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1995:35584 BIOSIS
DN PREV199598049884
TI Elevated expression of Th1 cytokines and **nitric oxide** synthase in the lungs of vaccinated mice after challenge infection with Schistosoma mansoni.
AU Wynn, Thomas A. (1); Oswald, Isabelle P.; Eltoum, Isam A.; Caspar, Patricia; Lowenstein, Charles J.; Lewis, Fred A.; James, Stephanie L.; Sher, Alan
CS (1) 9000 Rockville Pike, Natl. Inst. Health, Building 4, Room 126, Bethesda, MD 20892 USA
SO Journal of Immunology, (1994) Vol. 153, No. 11, pp. 5200-5209. ISSN: 0022-1767.
DT Article
LA English
AB C57BL/6 mice were vaccinated with irradiated cercariae of Schistosoma mansoni, and, at various times after challenge infection, total lung mRNA was isolated to assess the induction of several cytokines that previously had been shown in in vitro studies to be involved in the activation of macrophages and/or endothelial cells for **nitric oxide** (NO) production and killing of schistosomula. Vaccinated mice demonstrated
a highly significant increase in IFN-gamma mRNA upon subsequent infection when compared with infected nonvaccinated controls. A similar, although less dramatic, increase in two other macrophage-activating cytokines, TNF-alpha and IL-2, also was observed. In contrast, although the Th2 cytokines IL-4, IL-5, IL-10, and IL-13 were elevated in challenged vaccinated animals, only IL-10 and IL-13 showed increases that were significant with respect to the mRNA levels observed in challenged controls. Neutralization of IFN-gamma reduced immunity in vaccinated animals and resulted in decreased IFN-gamma, IL-2, IL-10, TNF-alpha, and IL-12 p40 but markedly increased IL-4, IL-5, and IL-13 mRNA expression and
serum IgE levels. Pulmonary **NO synthase** expression was elevated in immunized mice at a time at which immune elimination of schistosomula is believed to occur. Moreover, suppression of **NO synthase** activity with the inhibitor aminoguanidine reduced

immunity, as measured by a 32 to 33% increase in worm burden. Together, these data support previous in vitro studies that suggest a role for NO in schistosomulum killing. Furthermore, the observation that the down-regulatory cytokines IL-4, IL-10, and IL-13 are induced together with IFN-gamma may provide an explanation for the failure of this **vaccine** to provide complete protection.

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Parasitology; Respiratory System (Respiration)

IT Chemicals & Biochemicals
NITRIC OXIDE SYNTHASE

IT Miscellaneous Descriptors
INTERFERON-GAMMA; INTERLEUKIN-10; **INTERLEUKIN-12**; INTERLEUKIN-13; INTERLEUKIN-2; INTERLEUKIN-4; INTERLEUKIN-5; TUMOR NECROSIS FACTOR-ALPHA

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Trematoda:
Platyhelminthes, Helminthes, Invertebrata, Animalia

ORGN Organism Name
Muridae (Muridae); Schistosoma mansoni (Trematoda)

ORGN Organism Superterms
animals; chordates; helminths; invertebrates; mammals; nonhuman mammals; nonhuman vertebrates; platyhelminths; rodents; vertebrates

RN **125978-95-2** (**NITRIC OXIDE** SYNTHASE)

L23 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS

AN 2001:47391 BIOSIS

DN PREV200100047391

TI Recombinant human **IL-12** promotes the anti-tumor activity of human tumor-infiltrating lymphocytes (TIL) through the induction of IFN-gamma and iNOS in a human tumor/TIL SCID mouse xenograft model.

AU Hess, S. D. (1); Egilmez, N. K. (1); Jong, Y. S.; Chen, F.-A. (1); Anderson, T. M. (1); Mathiowitz, E.; Bankert, R. B. (1)

CS (1) Roswell Park Cancer Institute, Buffalo, NY, 14263 USA

SO FASEB Journal, (April 20, 2000) Vol. 14, No. 6, pp. A1007. print.
Meeting Info.: Joint Annual Meeting of the American Association of Immunologists and the Clinical Immunology Society Seattle, Washington, USA
May 12-16, 2000
ISSN: 0892-6638.

DT Conference

LA English

SL English

IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Immune System (Chemical Coordination and Homeostasis); Tumor Biology

IT Parts, Structures, & Systems of Organisms

tumor-infiltrating lymphocytes: anti-tumor activity, blood and lymphatics, immune system
IT Chemicals & Biochemicals
IFN-gamma [interferon-gamma]: induction; **IL-12** [**interleukin-12**]: recombinant; N-nitro-L-arginine methyl ester [**L-NAME**]: iNOS inhibitor; iNOS [inducible nitric oxide synthase]; nitric oxide
IT Miscellaneous Descriptors
human tumor/tumor-infiltrating lymphocyte xenograft model; tumor microenvironment; tumor suppression; Meeting Abstract
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae:
Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
SCID mouse [severe combined immunodeficiency mouse] (Muridae): animal model; human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates
RN **50903-99-6** (N-NITRO-L-ARGININE METHYL ESTER)
50903-99-6 (**L-NAME**)
10102-43-9 (NITRIC OXIDE)

L23 ANSWER 2 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:132853 BIOSIS
DN PREV200000132853
TI The potentiated antileukemic effects of doxorubicin and **interleukin-12** combination are not dependent on nitric oxide production.
AU Zagozdzon, Radoslaw (1); Giermasz, Adam; Golab, Jakub; Stoklosa, Tomasz; Jalili, Ahmad; Jakobisiak, Marek
CS (1) Department of Immunology, Institute of Biostructure, Medical University of Warsaw, Chalubinskiego 5, 02-004, Warsaw Poland
SO Cancer Letters., (Dec. 1, 1999) Vol. 147, No. 1-2, pp. 67-75. ISSN: 0304-3835.
DT Article
LA English
SL English
AB In our recent study we described a significant antileukemic efficacy of a combination therapy with **interleukin-12** (**IL-12**) and doxorubicin (DOX) in the L1210 leukemia model. This therapeutic effect was abrogated by elimination of activated macrophages. Activated macrophages produce a variety of factors that can contribute to the elimination of tumor cells in vivo, including proteases, TNF, reactive oxygen intermediates, and nitric oxide (NO). Based on the results of previous reports, the contribution of NO in potentiated antileukemic effects of **IL-12** + DOX combination seemed to be highly possible. Both DOX and **IL-12** given alone increased the production of NO by peritoneal macrophages, however, macrophages derived from the mice treated with the combination of those agents produced significantly less NO than macrophages from **IL-12** -alone-treated mice. Production of NO by spleen macrophages after **IL-12** + DOX treatment was higher than it was in controls, **IL-12**-alone-or DOX-alone-treated groups. In serum, concentrations of NOx- in **IL-12**- or **IL**

-12 + DOX-treated mice were significantly higher in comparison with controls, however not significantly different from each other. Addition of **L-NAME** treatment to the **IL-12** + DOX therapy in leukemia-bearing mice did not significantly change the antileukemic efficacy of this therapy. Thus, our results indicate that the augmented antileukemic effects of **IL-12** + DOX combination therapy in L1210 model are NO-independent. Therefore, further studies on the possible mechanisms of potentiated antileukemic activity of combination of **IL-12** and DOX would be worth pursuing.

IT Major Concepts
Pharmacology; Tumor Biology
IT Parts, Structures, & Systems of Organisms
macrophage: blood and lymphatics, immune system
IT Diseases
leukemia: blood and lymphatic disease, neoplastic disease
IT Chemicals & Biochemicals
doxorubicin: antineoplastic - drug, combination therapy; **interleukin-12**: antineoplastic - drug, combination therapy; nitric oxide: production; reactive oxygen intermediates; tumor necrosis factor
IT Alternate Indexing
Leukemia (MeSH)
IT Methods & Equipment
chemoimmunotherapy: therapeutic method
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
L1210 cell line (Muridae): animal model; mouse (Muridae)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 23214-92-8 (DOXORUBICIN)
10102-43-9 (NITRIC OXIDE)

L23 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:232593 BIOSIS
DN PREV199900232593
TI CD40 ligation prevents Trypanosoma cruzi infection through **interleukin-12** upregulation.
AU Chaussabel, Damien; Jacobs, Frederique; De Jonge, Jan; De Veerman, Marijke; Carlier, Yves; Thielemans, Kris; Goldman, Michel; Vray, Bernard (1)
CS (1) Laboratoire d'Immunologie Experimentale, Faculte de Medecine, Universite Libre de Bruxelles, route de Lennik, B-1070, Brussels Belgium
SO Infection and Immunity, (April, 1999) Vol. 67, No. 4, pp. 1929-1934. ISSN: 0019-9567.
DT Article
LA English
SL English
AB Because of the critical role of the CD40-CD40 ligand (CD40L) pathway in the induction and effector phases of immune responses, we investigated the effects of CD40 ligation on the control of Trypanosoma cruzi infection. First, we observed that supernatants of murine spleen cells stimulated by CD40L-transfected 3T3 fibroblasts (3T3-CD40L transfectants) prevent the

infection of mouse peritoneal macrophages (MPM) by T. cruzi. This phenomenon depends on de novo production of nitric oxide (NO) as it is prevented by the addition of N-nitro-L-arginine methyl ester, a NO synthase inhibitor. NO production requires interleukin (**IL**)-**12**-mediated gamma interferon (IFN-gamma) and tumor necrosis factor alpha (TNF-alpha) synthesis as demonstrated by inhibition experiments using neutralizing anti-**IL-12**, anti-IFN-gamma, and anti-TNF-alpha monoclonal antibodies (MAb). We found that an activating anti-CD40 MAb also directly stimulates IFN-gamma-activated MPM to produce NO and thereby to control T. cruzi infection. To determine the in vivo relevance of these in vitro findings, mice were injected with 3T3-CD40L transfectants or 3T3 control fibroblasts at the time of T. cruzi inoculation. We observed that in vivo CD40 ligation dramatically reduced both parasitemia and the mortality rate of T. cruzi-infected mice. A reduced parasitemia was still observed when the injection of 3T3-CD40L transfectants was delayed 8 days postinfection. It was abolished by injection of anti-**IL-12** MAb. Taken together, these data establish that CD40 ligation facilitates the control of T. cruzi infection through a cascade involving **IL-12**, IFN-gamma, and NO.

IT Major Concepts
Immune System (Chemical Coordination and Homeostasis); Parasitology
IT Parts, Structures, & Systems of Organisms
peritoneal macrophage: blood and lymphatics, immune system; spleen cells: blood and lymphatics, immune system
IT Diseases
Trypanosoma cruzi infection: parasitic disease
IT Chemicals & Biochemicals
gamma interferon; **interleukin-12**: upregulation; nitric oxide: production; tumor necrosis factor alpha; CD40; CD40 ligand; N-nitro-L-arginine methyl ester: nitric oxide synthase inhibitor
IT Miscellaneous Descriptors
immune response
ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
murine (Muridae); Trypanosoma cruzi (Flagellata): pathogen; 3T3 cell line (Muridae): murine fibroblast cells
ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates
RN 10102-43-9 (NITRIC OXIDE)
50903-99-6 (N-NITRO-L-ARGININE METHYL ESTER)
125978-95-2 (NITRIC OXIDE SYNTHASE)

L23 ANSWER 4 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:56046 BIOSIS
DN PREV199900056046
TI Nitric oxide regulates Th1 cell development through the inhibition of **IL-12** synthesis by macrophages.
AU Huang, Fang-Ping; Niedbala, Wanda; Wei, Xiao-Qing; Xu, Damo; Feng, Gui-Jie; Robinson, John H.; Lam, Charles; Liew, Foo Y. (1)
CS (1) Dep. Immunol., Univ. Glasgow, Glasgow G11 6NT UK
SO European Journal of Immunology, (Dec., 1998) Vol. 28, No. 12, pp. 4062-4070.

ISSN: 0014-2980.
DT Article
LA English
AB We have previously reported that mice lacking inducible nitric oxide synthase (NOS2) developed enhanced Th1 cell responses. We now investigated the mechanism by which NO modulates Th1 cells differentiation. Peritoneal macrophages from NOS2-deficient mice infected with Leishmania major in vivo or stimulated with IFN-gamma or lipopolysaccharide (LPS) in vitro produced significantly higher levels of **IL-12** than those from heterozygous or wild-type mice. A macrophage cell line, J774, produced significant amounts of **IL-12** following activation with LPS, or LPS plus IFN-gamma. This could be markedly enhanced by the NOS inhibitor L-NG monomethyl arginine (**L-NMMA**), but profoundly inhibited by the NO-generating compound S-nitroso-N-acetyl-penicillamine (SNAP). The effect of NO in this system is selective, since SNAP enhanced and **L-NMMA** decreased TNF-alpha synthesis by LPS-activated J774 cells. The differential effect of NO on **IL-12** and TNF-alpha is at the transcriptional level and is activation dependent. Since **IL-12** is a major inducer of Th1 cells which produce IFN-gamma that can activate macrophages to produce **IL-12**, our data demonstrate that NO can be an inhibitor of this feedback loop, preventing the excessive amplification of Th1 cells which are implicated in a range of immunopathologies.
IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis); Parasitology
IT Parts, Structures, & Systems of Organisms
peritoneal macrophage: blood and lymphatics, immune system
IT Chemicals & Biochemicals
interferon gamma; lipopolysaccharide; nitric oxide; nitric oxide synthase; tumor necrosis factor-alpha; **IL-12** [**interleukin-12**]; L-N G monomethyl arginine: nitric oxide synthase inhibitor; S-nitroso-N-acetyl-penicillamine: nitric oxide generating compound
IT Miscellaneous Descriptors
Th1 cell response
ORGN Super Taxa
Flagellata: Protozoa, Invertebrata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
mouse (Muridae); J774 cell line (Muridae); Leishmania major (Flagellata): parasite
ORGN Organism Superterms
Animals; Chordates; Invertebrates; Mammals; Microorganisms; Nonhuman Mammals; Nonhuman Vertebrates; Protozoans; Rodents; Vertebrates
RN 10102-43-9 (NITRIC OXIDE)
125978-95-2 (NITRIC OXIDE SYNTHASE)
79032-48-7 (S-NITROSO-N-ACETYL-PENICILLAMINE)
74-79-3Q (ARGININE)
7200-25-1Q (ARGININE)

L23 ANSWER 5 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:41234 BIOSIS
DN PREV199900041234
TI Collagen deposition in a non-fibrotic lung granuloma model after nitric

oxide inhibition.
AU Hogaboam, Cory M. (1); Gallinat, Chad S.; Bone-Larson, Cynthia; Chensue, Stephen W.; Lukacs, Nicholas W.; Strieter, Robert M.; Kunkel, Steven L.
CS (1) Dep. Pathol., Univ. Michigan Med. Sch., 1301 Catherine Road, Ann Arbor, MI 48109-0602 USA
SO American Journal of Pathology, (Dec., 1998) Vol. 153, No. 6, pp. 1861-1872.
ISSN: 0002-9440.
DT Article
LA English
AB Recent studies support the concept that pulmonary granulomatous inflammation directed by interferon (IFN)-gamma, interleukin (**IL**)**-12**, and nitric oxide usually resolves in the absence of fibrosis. To determine whether nitric oxide participates in modulating the fibrotic response during the development of pulmonary granulomas in response to purified protein derivative (PPD), mice presensitized to PPD received daily intraperitoneal injections of NG-nitro-D-arginine-methyl ester (D-NAME), N-nitro-L-arginine-methyl ester (**L-NAME**), or aminoguanidine after delivery of PPD-coated beads to the lungs. Eight days later, morphometric analysis of lung granulomas revealed that **L-NAME**-treated mice when challenged with PPD in vitro for 36 hours had the largest pulmonary granulomas and the greatest collagen deposition among the treated groups. in addition, equivalent numbers of dispersed lung cells from **L-NAME**- and aminoguanidine-treated mice produced significantly higher levels of IL-4, monocyte chemoattractant protein (MCP)-1, and macrophage inflammatory protein (MIP)-1alpha and significantly lower levels of eotaxin compared with D-NAME-treated mice. Cultures of dispersed lung cells from **L-NAME**-treated mice also produced significantly more IL-10 and less **IL-12** compared with similar numbers of dispersed lung cells from D-NAME-treated mice. Cultures of isolated lung fibroblasts from **L-NAME**-treated mice expressed higher levels of C-C chemokine receptor 2 (CCR2) and CCR3 mRNA and contained less MCP-1 and eotaxin protein than a similar number of fibroblasts from D-NAME-treated mice. Thus, nitric oxide appears to regulate the deposition of extracellular matrix in lung granulomas through the modulation of the cytokine and chemokine profile of these lesions. Alterations in the cytokine, chemokine, and procollagen profile of this lesion may be a direct effect of nitric oxide on the pulmonary fibroblast and provide an Important signal for regulating fibroblast activity during the evolution of chronic lung disease.
IT Major Concepts
Respiratory System (Respiration)
IT Parts, Structures, & Systems of Organisms
lungs: respiratory system
IT Diseases
non-fibrotic lung granuloma: respiratory system disease
IT Chemicals & Biochemicals
collagen; interferon-gamma; interleukin-10; **interleukin-12**; interleukin-4; macrophage inflammatory protein-1alpha; monocyte chemoattractant protein-1; nitric oxide; purified protein derivative
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
mouse (Muridae): model
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN 10102-43-9 (NITRIC OXIDE)

L23 ANSWER 6 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1998:496780 BIOSIS
DN PREV199800496780
TI Increased nitric oxide (NO) production by antigen-presenting dendritic cells is responsible for low allogeneic mixed leucocyte reaction (MLR) in primary biliary cirrhosis (PBC.
AU Yamamoto, K. (1); Fazle Akbar, S. M.; Masumoto, T.; Onji, M.
CS (1) Third Dep. Intern. Med., Ehime Univ. Sch. Med., Shigenobu-Cho, Ehime 791-0295 Japan
SO Clinical and Experimental Immunology, (Oct., 1998) Vol. 114, No. 1, pp. 94-101.
ISSN: 0009-9104.
DT Article
LA English
AB The levels of blastogenesis in allogeneic MLR containing T cells from one normal volunteer and irradiated dendritic cells from 29 patients with PBC,
17 patients with chronic hepatitis type C (CH-C) and 22 allogeneic normal controls were compared to see if there is any role of antigen-presenting cells (APC) in the pathogenesis of PBC. The stimulatory capacity of dendritic cells from PBC was significantly lower compared with that of dendritic cells from CH-C ($P<0.05$) and normal controls ($P < 0.05$), which could not be attributable either to the levels of expression of surface molecules, such as HLA-DR and CD86 on dendritic cells, or to the levels of
cytokines, such as IL-10 and **IL-12**. Significantly
higher levels of NO were seen in the allogeneic MLR supernatants containing dendritic cells from PBC compared with the supernatants from cultures containing dendritic cells from CH-C ($P<0.001$) or normal controls
($P<0.001$). Moreover, dendritic cells from PBC produced 10 times more NO compared with dendritic cells from CH-C and normal controls (21.9 +- 2.8 muM versus 1.6 +- 0.3 muM and 1.6 +- 0.3 muM, respectively; $P < 0.001$). The addition of NG-monomethyl-L-arginine monoacetate (LNMMA), a known inhibitor of NO in allogeneic MLR containing dendritic cells from PBC, resulted in a significant decrease of NO and increase of blastogenesis. The selective impairment of dendritic cell function, increased production of NO by dendritic cells and restoration of blastogenesis using NO inhibitor in PBC have suggested a role for NO and dysfunction of dendritic
cells in the pathogenesis of PBC. This inspires optimism that modulating the function of dendritic cells and controlling NO production, an improved
therapeutic approach, might be planned for PBC.
IT Major Concepts
Digestive System; Immune System (Chemical Coordination and Homeostasis)
IT Parts, Structures, & Systems of Organisms
dendritic cell: antigen-presenting, immune system
IT Diseases

primary biliary cirrhosis: digestive system disease, pathogenesis
IT Chemicals & Biochemicals
interleukin-10; **interleukin-12**; nitric oxide: production; CD86; HLA-DR; N-G-monomethyl-L-arginine
IT Miscellaneous Descriptors
mixed leukocyte reaction: allogeneic, low
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 10102-43-9 (NITRIC OXIDE)
17035-90-4 (N-G-MONOMETHYL-L-ARGININE)

L23 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:77379 BIOSIS
DN PREV199698649514
TI Production of nitric oxide (NO) is not essential for protection against acute Toxoplasma gondii infection in IRF-1-/- mice.
AU Khan, Imtiaz A. (1); Matsuura, Tadashi; Fonseka, Sujeewa; Kasper, Lloyd H.
CS (1) Dep. Med., Dartmouth Medical School, Vail 212, Hanover, NH 03755 USA
SO Journal of Immunology, (1996) Vol. 156, No. 2, pp. 636-643.
ISSN: 0022-1767.
DT Article
LA English
AB Production of nitric oxide (NO) by macrophages is important for the killing of intracellular pathogens. IFN-gamma and LPS stimulate NO production by transcriptional up-regulation of inducible nitric oxide synthetase (iNOS). In the present study we used mice with a targeted disruption of the IFN regulatory factor-1 gene (IRF-1-/-) to investigate the importance of NO in the host immune response against Toxoplasma gondii, a major cause of infection in newborns and those with AIDS. IRF-1-/- mice were more susceptible to acute Toxoplasma infection, and treatment with either exogenous IFN-gamma or in vivo neutralization of endogenous IFN-gamma had little effect on their susceptibility to infection. However, administration of exogenous **IL-12** was able to prolong survival even when IFN-gamma was depleted. An in vivo depletion study suggested that the mechanism of this protective response is mediated in part by CD4+ T cells. The administration of IL-1 2 could not overcome the inhibition of lymphoproliferative response in T. gondii-infected mice and treatment with N-monomethyl-L-arginine (**L-NMMA**), a nitric oxide synthase (iNOS) antagonist in vitro was unable to reverse the immunosuppression. In response to Toxoplasma infection, splenocytes from IRF-1-/- mice exhibited increased production of IL-10 as well as a 30-fold increase in its message expression. These studies indicate that NO may not be essential for host immunity to the parasite, and moreover that **IL-12** appears to induce an IFN-gamma-independent mechanism of protection against this opportunistic pathogen.
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Genetics; Immune System (Chemical Coordination and Homeostasis); Metabolism; Parasitology
IT Chemicals & Biochemicals
NITRIC OXIDE

IT Miscellaneous Descriptors
INTERFERON REGULATORY FACTOR-1 GENE; **INTERLEUKIN-12** ; OPPORTUNISTIC PATHOGEN; PARASITE HOST IMMUNITY
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Sporozoa: Invertebrata, Protozoa, Animalia
ORGN Organism Name
Muridae (Muridae); Toxoplasma gondii (Sporozoa)
ORGN Organism Superterms
animals; chordates; invertebrates; mammals; microorganisms; nonhuman mammals; nonhuman vertebrates; protozoans; rodents; vertebrates
RN 10102-43-9 (NITRIC OXIDE)

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=> fil medline

FILE 'MEDLINE' ENTERED AT 11:23:48 ON 22 FEB 2001

 FILE LAST UPDATED: 27 OCT 2000 (20001027/UP).  FILE COVERS 1960 TO DATE.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2000 vocabulary.  Enter HELP THESAURUS for details.

 The OLDMEDLINE file segment now contains data from 1958 through 1965.
 Enter HELP CONTENT for details.

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 Basic Index.  See HELP SFIELDS for details.

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 COMPLETED.  NOTICE WILL BE GIVEN ONCE THE RELOAD IS COMPLETED AND
 RELOAD DETAILS WILL BE FOUND IN HELP RLOAD.

=> d his l1-l12


     (FILE 'MEDLINE' ENTERED AT 11:13:00 ON 22 FEB 2001)
                DEL HIS Y
L1            0 S INTERLEUKIN'-'12CT
L2         2762 S INTERLEUKIN'-'12/CT
L3        21589 S NITRIC OXIDE/CT
L4        10800 S NITRIC'-'OXIDE SYNTHASE+NT/CT
L5        27423 S L3 OR L4
L6         6321 S L5 (L) AI./CT
L7           21 S L6 AND L2
                E NG-NITROARGININE METHYL ESTER/CT
                E E3+ALL
                E L-NMMA/CT
                E E3+ALL
L8         2943 S NG'-'NITROARGININE METHYL ESTER/CT
L9         1269 S OMEGA'-'N'-'METHYLARGININE/CT
L10        4098 S L8 OR L9
L11           6 S L10 AND L2
L12          23 S L11 OR L7

=> d .med l12 1-23


L12  ANSWER 1 OF 23  MEDLINE
AN   2000123487     MEDLINE
DN   20123487
TI   The potentiated antileukemic effects of doxorubicin and interleukin-12
     combination are not dependent on nitric oxide production.
AU   Zagozdzon R; Giermasz A; Golab J; Stoklosa T; Jalili A; Jakobisiak M
CS   Department of Immunology, Institute of Biostructure, Medical University
of
     Warsaw, Poland.. rzagozd@ib.amwaw.edu.pl
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SO CANCER LETTERS, (1999 Dec 1) 147 (1-2) 67-75.
Journal code: CMX. ISSN: 0304-3835.
CY Ireland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 200005
EW 20000501

AB In our recent study we described a significant antileukemic efficacy of a combination therapy with interleukin-12 (IL-12) and doxorubicin (DOX) in the L1210 leukemia model. This therapeutic effect was abrogated by elimination of activated macrophages. Activated macrophages produce a variety of factors that can contribute to the elimination of tumor cells in vivo, including proteases, TNF, reactive oxygen intermediates, and nitric oxide (NO). Based on the results of previous reports, the contribution of NO in potentiated antileukemic effects of IL-12 + DOX combination seemed to be highly possible. Both DOX and IL-12 given alone increased the production of NO by peritoneal macrophages, however, macrophages derived from the mice treated with the combination of those agents produced significantly less NO than macrophages from IL-12-alone-treated mice. Production of NO by spleen macrophages after IL-12 + DOX treatment was higher than it was in controls, IL-12-alone or DOX-alone-treated groups. In serum, concentrations of NOx- in IL-12- or IL-12 + DOX-treated mice were significantly higher in comparison with controls, however not significantly different from each other. Addition of
L-NAME treatment to the IL-12 + DOX therapy in leukemia-bearing mice did not significantly change the antileukemic efficacy of this therapy. Thus, our results indicate that the augmented antileukemic effects of IL-12 + DOX combination therapy in L1210 model are NO-independent. Therefore, further studies on the possible mechanisms of potentiated antileukemic activity of combination of IL-12 and DOX would be worth pursuing.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Adjuvants, Immunologic: AD, administration & dosage
Antibiotics, Anthracycline: AD, administration & dosage
*Antineoplastic Agents, Combined: TU, therapeutic use
Cells, Cultured
Crosses, Genetic
Doxorubicin: AD, administration & dosage
Drug Synergism
Enzyme Inhibitors: PD, pharmacology
Interleukin-12: AD, administration & dosage
*Leukemia L1210: DT, drug therapy
Leukemia L1210: IM, immunology
*Leukemia L1210: ME, metabolism
Leukemia L1210: PA, pathology
Macrophages, Peritoneal: DE, drug effects
Macrophages, Peritoneal: IM, immunology
Macrophages, Peritoneal: ME, metabolism
Mice
Mice, Inbred C57BL
Mice, Inbred DBA
Neoplasm Transplantation
Nitrates: BL, blood
*Nitric Oxide: BI, biosynthesis
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitrites: BL, blood

NG-Nitroarginine Methyl Ester: PD, pharmacology
Spleen: DE, drug effects
Spleen: ME, metabolism
Survival Rate

L12 ANSWER 2 OF 23 MEDLINE
AN 2000103831 MEDLINE
DN 20103831
TI Antifungal type 1 responses are upregulated in IL-10-deficient mice.
AU Del Sero G; Mencacci A; Cenci E; d'Ostiani C F; Montagnoli C; Bacci A; Mosci P; Kopf M; Romani L
CS Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Italy.
SO Microbes Infect, (1999 Dec) 1 (14) 1169-80.
Journal code: DJ1. ISSN: 1286-4579.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200004
EW 20000404
AB C57BL/6 mice are highly resistant to infections caused by Candida albicans and Aspergillus fumigatus. To elucidate the role of IL-10 produced by C57BL/6 mice during these infections, parameters of infection and immunity to it were evaluated in IL-10-deficient and wild-type mice with disseminated or gastrointestinal candidiasis or invasive pulmonary aspergillosis. Unlike parasitic protozoan infection, C. albicans or A. fumigatus infection did not induce significant acute toxicity in IL-10-deficient mice, who, instead, showed reduced fungal burden and fungal-associated inflammatory responses. The increased resistance to infections as compared to wild-type mice was associated with upregulation of innate and acquired antifungal Th1 responses, such as a dramatically higher production of IL-12, nitric oxide (NO) and TNF-alpha as well as IFN-gamma by CD4+ T cells. Pharmacological inhibition of NO production greatly reduced resistance to gastrointestinal candidiasis, thus pointing to the importance of IL-10-dependent NO regulation at mucosal sites in fungal infections. These results are reminiscent of those obtained in genetically susceptible mice, in which IL-10 administration increased, and IL-10 neutralization decreased, susceptibility to C. albicans and A. fumigatus infections. Collectively, these observations indicate that the absence of IL-10 augments innate and acquired antifungal immunity by upregulating type 1 cytokine responses. The resulting protective Th1 responses lead to a prompt reduction of fungal growth, thus preventing tissue destruction and lethal levels of proinflammatory cytokines.
CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't
Antigens, CD4: ME, metabolism
Aspergillus fumigatus
Candida albicans
Enzyme-Linked Immunosorbent Assay
Guanidines: PD, pharmacology
Immunity, Cellular
Immunity, Natural
Inflammation
Interferon Type II: ME, metabolism

Interleukin-10: GE, genetics
Interleukin-10: ME, metabolism
*Interleukin-10: PH, physiology
Interleukin-12: ME, metabolism
Mice
Mice, Inbred C57BL
Mice, Knockout
*Mycoses: IM, immunology
Mycoses: MI, microbiology
Mycoses: PA, pathology
Nitric Oxide: AI, antagonists & inhibitors
Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Polymerase Chain Reaction
RNA, Messenger: AN, analysis
Th1 Cells: IM, immunology
*Th1 Cells: ME, metabolism
Tumor Necrosis Factor: ME, metabolism

L12 ANSWER 3 OF 23 MEDLINE
AN 2000087332 MEDLINE
DN 20087332
TI Role of interferon-gamma and nitric oxide in pulmonary edema and death induced by lipopolysaccharide.
AU Heremans H; Dillen C; Groenen M; Matthys P; Billiau A
CS Laboratory of Immunobiology, Rega Institute, University of Leuven, Faculty of Medicine, Leuven, Belgium.. Hubertine.Heremans@rega.kuleuven.ac.be
SO AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (2000 Jan) 161 (1) 110-7.
Journal code: BZS. ISSN: 1073-449X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200005
EW 20000501
AB Mice given lipopolysaccharide (LPS) intravenously developed lung edema, which was maximum after 6 h. Tumor necrosis factor, interleukin 12 (IL-12), IL-6, and interferon-gamma (IFN-gamma) appeared in the serum, and levels of nitrogen oxide (NO) derivatives were increased in serum and bronchoalveolar fluid. Mice pretreated with neutralizing anti-IFN-gamma antibodies had lower serum levels of IFN-gamma, and fewer died. However, levels of other cytokines and NO derivatives as well as lung edema were unchanged. If IFN-gamma and LPS were given together, pulmonary edema was less, but levels of cytokines and NO derivatives in serum were raised, and the mortality was greater. IFN-gamma receptor knockout mice had more edema after LPS, but were less sensitive to the lethal effects. Treatment with anti-IL-12 antibody inhibited IFN-gamma induction and reduced mortality, but had no effect on the lung edema; exogenous IL-12 also failed to affect edema, but boosted serum cytokine levels and increased the mortality. Aminoguanidine, an inhibitor of NO synthase, protected against pulmonary

edema, but did not modify the lethal effects of LPS. Clearly, in this model, early pulmonary edema and lethality are not directly related, and induced IFN-gamma has no role in causing early lung edema, but augments other events that result in death.

CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't
Bronchoalveolar Lavage Fluid: CH, chemistry
Disease Models, Animal
Enzyme Inhibitors: PD, pharmacology
Guanidines: PD, pharmacology
Interferon-alpha: PD, pharmacology
*Interferon-alpha: PH, physiology
Interleukin-12: ME, metabolism
Interleukin-6: ME, metabolism
*Lipopolysaccharides: TO, toxicity
Mice
Mice, Inbred Strains
*Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Pulmonary Edema: CI, chemically induced
*Pulmonary Edema: ME, metabolism
Pulmonary Edema: MO, mortality
Pulmonary Edema: PC, prevention & control
*Serratia marcescens
Tumor Necrosis Factor: ME, metabolism

L12 ANSWER 4 OF 23 MEDLINE
AN 1999388002 MEDLINE
DN 99388002
TI Effects of nitric oxide on the induction and differentiation of Th1 cells.
AU Niedbala W; Wei X Q; Piedrafita D; Xu D; Liew F Y
CS Department of Immunology, University of Glasgow, Glasgow, GB.
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Aug) 29 (8) 2498-505.
Journal code: EN5. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199911
EW 19991104
AB We have previously shown that mice lacking inducible NO synthase are markedly more susceptible to Leishmania major infection but developed a significantly enhanced Th1 cell response compared with wild-type mice. Furthermore, at high concentrations, NO inhibited IL-12 synthesis by activated macrophages, thereby indirectly suppressing the expansion of Th1 cells. We report here that at low concentrations, NO selectively enhanced the induction of Th1 cells and had no effect on Th2 cells. NO exerted this effect in synergy with IL-12 during Th1 cell differentiation and had no effect on fully committed Th1 cells. NO appears to affect CD4(+) T cells directly and not at the antigen-presenting cells. These results therefore provide an additional pathway by which NO modulates the immune response and contributes to the homeostasis of the immune system.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Cell Differentiation: DE, drug effects
Clone Cells

CD4-Positive T-Lymphocytes: CY, cytology
CD4-Positive T-Lymphocytes: DE, drug effects
CD4-Positive T-Lymphocytes: IM, immunology
Drug Synergism
Enzyme Inhibitors: PD, pharmacology
Interleukin-12: AD, administration & dosage
Interleukin-12: PD, pharmacology
Leishmania major
Leishmaniasis, Cutaneous: ET, etiology
Leishmaniasis, Cutaneous: IM, immunology
Lymphocyte Transformation
Lysine: AA, analogs & derivatives
Lysine: PD, pharmacology
Mice
Mice, Inbred BALB C
Mice, Knockout
Nitric Oxide: AD, administration & dosage
*Nitric Oxide: PD, pharmacology
Nitric Oxide Donors: PD, pharmacology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: DF, deficiency
Nitric-Oxide Synthase: GE, genetics
Penicillamine: AA, analogs & derivatives
Penicillamine: PD, pharmacology
Th1 Cells: CY, cytology
*Th1 Cells: DE, drug effects
*Th1 Cells: IM, immunology

L12 ANSWER 5 OF 23 MEDLINE
AN 1999369977 MEDLINE
DN 99369977
TI Bruton's tyrosine kinase deficiency in macrophages inhibits nitric oxide generation leading to enhancement of IL-12 induction.
AU Mukhopadhyay S; George A; Bal V; Ravindran B; Rath S
CS National Institute of Immunology, New Delhi, India.
SO JOURNAL OF IMMUNOLOGY, (1999 Aug 15) 163 (4) 1786-92.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199911
EW 19991102
AB We show that macrophages of X-linked immunodeficient mice with a mutant nonfunctional Bruton's tyrosine kinase produce less NO than wild-type macrophages in response to a variety of stimuli. Induction of the inducible NO synthase (iNOS) protein, the transcription factor IFN regulatory factor-1 involved in iNOS expression, and the transcription factor STAT-1 involved in regulating IFN regulatory factor-1 induction are all poorer in X-linked immunodeficient than in wild-type macrophages. On the other hand, induction of IL-12 is higher in X-linked immunodeficient than in wild-type macrophages. Macrophage IL-12 induction is enhanced by iNOS inhibitors such as aminoguanidine and thiocitrulline and is inhibited by NO generation via sodium nitroprusside. There is relative enhancement of IFN-gamma production by immune T cells from mice immunized under

aminoguanidine cover. Our data thus suggest that Bruton's tyrosine kinase participates in signaling for iNOS induction via IFN regulatory factor-1 in macrophages and that NO is an inhibitor of IL-12 induction.

CT Check Tags: Animal; Support, Non-U.S. Gov't
Chickens
Conalbumin: AD, administration & dosage
Conalbumin: IM, immunology
DNA-Binding Proteins: BI, biosynthesis
DNA-Binding Proteins: GE, genetics
Enzyme Inhibitors: PD, pharmacology
Guanidines: PD, pharmacology
Immunologic Deficiency Syndromes: EN, enzymology
Immunologic Deficiency Syndromes: GE, genetics
Interleukin-12: AI, antagonists & inhibitors
***Interleukin-12: BI, biosynthesis**
Lymphocyte Transformation: GE, genetics
*Macrophages, Peritoneal: EN, enzymology
Macrophages, Peritoneal: IM, immunology
Macrophages, Peritoneal: ME, metabolism
Mice
Mice, Inbred CBA
Mice, Mutant Strains
***Nitric Oxide: AI, antagonists & inhibitors**
*Nitric Oxide: BI, biosynthesis
Nitric Oxide: PD, pharmacology
Nitric-Oxide Synthase: BI, biosynthesis
Nitric-Oxide Synthase: DF, deficiency
Nitric-Oxide Synthase: GE, genetics
Phosphoproteins: BI, biosynthesis
Phosphoproteins: GE, genetics
*Protein-Tyrosine Kinase: DF, deficiency
*Protein-Tyrosine Kinase: GE, genetics
T-Lymphocytes: IM, immunology
Trans-Activators: BI, biosynthesis
Trans-Activators: GE, genetics

L12 ANSWER 6 OF 23 MEDLINE
AN 1999255858 MEDLINE
DN 99255858
TI Requirement for type 2 NO synthase for IL-12 signaling in innate immunity [published erratum appears in Science 1999 Jun 11;284(5421):1776].
AU Diefenbach A; Schindler H; Rollinghoff M; Yokoyama W M; Bogdan C
CS Institut fur Klinische Mikrobiologie, Immunologie und Hygiene, Universitat
Erlangen, Wasserturmstrasse 3, D-91054 Erlangen, Germany.
SO SCIENCE, (1999 May 7) 284 (5416) 951-5.
Journal code: UJ7. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199908
AB Interleukin-12 (IL-12) and type 2 NO synthase (NOS2) are crucial for defense against bacterial and parasitic pathogens, but their relationship in innate immunity is unknown. In the absence of NOS2 activity, IL-12 was unable to prevent spreading of Leishmania parasites, did not stimulate natural killer (NK) cells for cytotoxicity or interferon-gamma (IFN-gamma)

release, and failed to activate Tyk2 kinase and to tyrosine phosphorylate Stat4 (the central signal transducer of IL-12) in NK cells. Activation of Tyk2 in NK cells by IFN-alpha/beta also required NOS2. Thus, NOS2-derived NO is a prerequisite for cytokine signaling and function in innate immunity.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Cells, Cultured
Cyclic GMP: ME, metabolism
Cytotoxicity, Immunologic
DNA-Binding Proteins: ME, metabolism
Enzyme Activation
Enzyme Inhibitors: PD, pharmacology
Immunity, Natural
Interferon Type II: BI, biosynthesis
Interferon Type II: GE, genetics
Interferons: PD, pharmacology
Interleukin-12: PD, pharmacology
***Interleukin-12: PH, physiology**
*Killer Cells, Natural: IM, immunology
Killer Cells, Natural: ME, metabolism
*Leishmania major
*Leishmaniasis, Cutaneous: IM, immunology
Leishmaniasis, Cutaneous: ME, metabolism
Lysine: AA, analogs & derivatives
Lysine: PD, pharmacology
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: AI, antagonists & inhibitors
*Nitric-Oxide Synthase: ME, metabolism
Phosphorylation
Protein-Tyrosine Kinase: ME, metabolism
Proteins: ME, metabolism
*Signal Transduction
Trans-Activators: ME, metabolism
Up-Regulation (Physiology)

L12 ANSWER 7 OF 23 MEDLINE
AN 1999244892 MEDLINE
DN 99244892
TI Different doses of adenoviral vector expressing IL-12 enhance or depress the immune response to a coadministered antigen: the role of nitric oxide.
AU Lasarte J J; Corrales F J; Casares N; Lopez-Diaz de Cerio A; Qian C; Xie X; Borras-Cuesta F; Prieto J
CS Department of Internal Medicine, Medical School and University Clinic, University of Navarra, Pamplona, Spain.
SO JOURNAL OF IMMUNOLOGY, (1999 May 1) 162 (9) 5270-7.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199907
EW 19990704
AB Joint immunization with two recombinant adenoviruses, one expressing

hepatitis C virus (HCV) core and E1 proteins and another expressing IL-12 (RAdIL-12), strongly potentiates cellular immune response against HCV Ags in BALB/c mice when RAdIL-12 was used at doses of 1 x 105-1 x 107 plaque-forming units. However, cellular immunity against HCV Ags was abolished when higher doses (1 x 108 plaque-forming units) of RAdIL-12 were used. This immunosuppressive effect was associated with marked elevation of IFN-gamma and nitric oxide in the serum and increased cell apoptosis in the spleen. Administration of N-nitro-L -arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, to mice that received high doses of RAdIL-12 was lethal, whereas no apparent systemic toxicity by L -NAME was observed in those immunized with lower doses of the adenovirus. Interestingly, in mice immunized with recombinant adenovirus expressing core and E1 proteins of HCV in combination with RAdIL-12 at low doses (1 x 107 plaque-forming units), L -NAME inhibited T cell proliferation and CTL activity in response to HCV Ags and also production of Abs against adenoviral proteins. In conclusion, gene transfer of IL-12 can increase or abolish cell immunity against an Ag depending of the dose of the vector expressing the cytokine. IL-12 stimulates the synthesis of NO which is needed for the immunostimulating effects of IL-12, but apoptosis of T cells and immunosuppression ensues when IFN-gamma and NO are generated at very high concentrations.

CT Check Tags: Animal; Support, Non-U.S. Gov't
*Adenoviridae: GE, genetics
*Adenoviridae: IM, immunology
Antibodies, Viral: BI, biosynthesis
Antigens, Viral: AD, administration & dosage
*Antigens, Viral: IM, immunology
Apoptosis: IM, immunology
Defective Viruses: GE, genetics
Defective Viruses: IM, immunology
Dose-Response Relationship, Immunologic
Epitopes, T-Lymphocyte: AD, administration & dosage
Epitopes, T-Lymphocyte: IM, immunology
Gene Expression Regulation: IM, immunology
Gene Transfer
*Genetic Vectors: AD, administration & dosage
Genetic Vectors: CS, chemical synthesis
*Genetic Vectors: IM, immunology
Hepatitis C-Like Viruses: IM, immunology
IgG: BI, biosynthesis
Injections, Intraperitoneal
Interferon Type II: BL, blood
Interleukin-12: BI, biosynthesis
Interleukin-12: BL, blood
***Interleukin-12: GE, genetics**
Mice
Mice, Inbred BALB C
Nitric Oxide: BI, biosynthesis
*Nitric Oxide: PH, physiology
NG-Nitroarginine Methyl Ester: AD, administration & dosage
Peritoneal Cavity: CY, cytology
Recombination, Genetic
Spleen: PA, pathology
T-Lymphocytes: DE, drug effects
T-Lymphocytes: IM, immunology
T-Lymphocytes: ME, metabolism
T-Lymphocytes, Cytotoxic: IM, immunology

Viral Core Proteins: GE, genetics
Viral Core Proteins: IM, immunology
Viral Envelope Proteins: GE, genetics
Viral Envelope Proteins: IM, immunology

L12 ANSWER 8 OF 23 MEDLINE
AN 1999128115 MEDLINE
DN 99128115
TI Strategies of protection from nitric oxide toxicity in islet inflammation.
AU Rothe H; Kolb H
CS Diabetes Research Institute at the Heinrich-Heine University of Dusseldorf, Germany.
SO JOURNAL OF MOLECULAR MEDICINE, (1999 Jan) 77 (1) 40-4. Ref: 51
Journal code: B8C. ISSN: 0946-2716.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199910
EW 19991003
AB Nitric oxide is thought to contribute to beta cell destruction during islet inflammation in animal models of type I diabetes. In vitro, inhibition of inducible nitric oxide synthase protects islet cells from the damaging effects of inflammatory cells or cytokines. However, the administration of several inducible nitric oxide synthase inhibitors to prediabetic animals had variable effects on disease progression. An alternative approach is to prevent the lethal consequences of nitric oxide action at the level of islet cells. We observed that the suppression of poly-(ADP-ribose)-polymerase ensures survival of islet cells exposed to nitric oxide. Cells could also be rendered resistant by the induction of endogenous stress proteins in particular of heat shock protein 70. Nitric oxide is not only a strong cytotoxic agent, but is also able to modulate immune reactions by interfering with Th1/Th2 reactivities. This may occur via induction of the interleukin-12 antagonist IL-12(p40)2. Development of type 1 diabetes is known to be correlated with a shift from a Th2 status during benign insulitis to a Th1 status during destructive insulitis. This shift was found dependent on local interleukin-12 gene expression. Indeed, administration of a natural interleukin-12 antagonist suppressed the progression of islet inflammation and concomitant upregulation of the inducible nitric oxide synthase.
CT Check Tags: Animal; Support, Non-U.S. Gov't
Diabetes Mellitus, Insulin-Dependent: DT, drug therapy
Diabetes Mellitus, Insulin-Dependent: IM, immunology
Diabetes Mellitus, Insulin-Dependent: PA, pathology
*Diabetes Mellitus, Insulin-Dependent: PP, physiopathology
Interleukin-12: AI, antagonists & inhibitors
Interleukin-12: PH, physiology
Islets of Langerhans: ME, metabolism
*Islets of Langerhans: PA, pathology
Mice

Mice, Inbred NOD
*Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
NAD+ ADP-Ribosyltransferase: ME, metabolism
T-Lymphocytes: IM, immunology

L12 ANSWER 9 OF 23 MEDLINE
AN 1999036420 MEDLINE
DN 99036420
TI Phlebotomus papatasi sand fly salivary gland lysate down-regulates a Th1, but up-regulates a Th2, response in mice infected with Leishmania major.
AU Mbow M L; Bleyenberg J A; Hall L R; Titus R G
CS Department of Pathology, Colorado State University College of Veterinary Medicine and Biomedical Sciences, Fort Collins 80523-1671, USA.
NC AI27511-09 (NIAID)
SO JOURNAL OF IMMUNOLOGY, (1998 Nov 15) 161 (10) 5571-7.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199902
EW 19990204
AB A vertebrate host becomes infected with Leishmania major when the sand fly vector injects parasites into skin along with saliva. Previous studies showed that salivary gland lysate of the New World sand fly Lutzomyia longipalpis markedly enhanced L. major infection in CBA mice. However, L. major is an Old World parasite transmitted in nature by the Old World sand fly Phlebotomus papatasi. Here we examine the ability of P. papatasi salivary gland lysate to enhance infection (lesion size and parasite burden) by L. major. In addition, we examine the effects of salivary gland lysate on the immune response to L. major by monitoring the levels of cytokine mRNA from the lymph nodes draining cutaneous lesions. We found that P. papatasi salivary gland lysate dramatically exacerbated lesion development in disease-resistant CBA mice. This exacerbation of disease correlated with inhibition of the production of Th1 cytokines and associated factors (IFN-gamma, IL-12, and inducible nitric oxide synthase), but with enhancement of the Th2 cytokine IL-4, whereas no changes in the levels of IL-10 and TGF-beta were noted. Importantly, salivary gland lysate directly up-regulated expression of IL-4 mRNA in mice in the absence of infection with L. major.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Down-Regulation (Physiology): IM, immunology
Interferon Type II: AI, antagonists & inhibitors
Interferon Type II: BI, biosynthesis
Interferon Type II: GE, genetics
Interleukin-10: BI, biosynthesis
Interleukin-10: GE, genetics
Interleukin-12: AI, antagonists & inhibitors
Interleukin-12: BI, biosynthesis
Interleukin-12: GE, genetics
Interleukin-4: BI, biosynthesis
Interleukin-4: GE, genetics

*Leishmania major: IM, immunology
*Leishmaniasis, Cutaneous: IM, immunology
Leishmaniasis, Cutaneous: PA, pathology
Leishmaniasis, Cutaneous: PS, parasitology
Lymph Nodes: EN, enzymology
Lymph Nodes: IM, immunology
Lymph Nodes: ME, metabolism
Mice
Mice, Inbred CBA
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: BI, biosynthesis
Nitric-Oxide Synthase: GE, genetics
*Phlebotomus: IM, immunology
RNA, Messenger: AI, antagonists & inhibitors
RNA, Messenger: BI, biosynthesis
Salivary Glands: CH, chemistry
*Salivary Glands: IM, immunology
*Th1 Cells: IM, immunology
Th1 Cells: ME, metabolism
*Th2 Cells: IM, immunology
Th2 Cells: ME, metabolism
Transforming Growth Factor beta: BI, biosynthesis
Transforming Growth Factor beta: GE, genetics
*Up-Regulation (Physiology): IM, immunology

L12 ANSWER 10 OF 23 MEDLINE
AN 1999021681 MEDLINE
DN 99021681
TI Immune suppression by recombinant interleukin (rIL)-12 involves interferon gamma induction of nitric oxide synthase 2 (iNOS) activity: inhibitors of NO generation reveal the extent of rIL-12 vaccine adjuvant effect.
AU Koblish H K; Hunter C A; Wysocka M; Trinchieri G; Lee W M
CS Cell and Molecular Biology Graduate Group, Cancer Center, and Institute for Human Gene Therapy, School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA.
NC AI-42334-01 (NIAID)
AI-34412 (NIAID)
CA 10815 (NCI)
+
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1998 Nov 2) 188 (9) 1603-10.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199902
EW 19990204
AB Recombinant interleukin 12 (IL-12) can profoundly suppress cellular immune responses in mice. To define the underlying mechanism, recombinant murine (rm)IL-12 was given to C57BL/6 mice undergoing alloimmunization and found to transiently but profoundly suppress in vivo and in vitro allogeneic responses and in vitro splenocyte mitogenic responses. Use of neutralizing antibodies and genetically deficient mice showed that IFN-gamma (but not TNF-alpha) mediated rmIL-12-induced immune suppression. Splenocyte

fractionation studies revealed that adherent cells from rmIL-12-treated mice suppressed the mitogenic response of normal nonadherent cells to concanavalin A and IL-2. Addition of an inhibitor of nitric oxide synthase (NOS) restored mitogenic responses, and inducible (i)NOS-/- mice were not immunosuppressed by rmIL-12. These results support the view that suppression of T cell responses is due to NO produced by macrophages responding to the high levels of IFN-gamma induced by rmIL-12. When a NOS inhibitor was given with rmIL-12 during vaccination of A/J mice with irradiated SCK tumor cells, immunosuppression was averted and the extent of rmIL-12's ability to enhance induction of protective antitumor immunity was revealed. This demonstrates that rmIL-12 is an effective vaccine adjuvant whose efficacy may be masked by its transient immunosuppressive effect.

CT Check Tags: Animal; Female; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.

Adjuvants, Immunologic: AD, administration & dosage
Adjuvants, Immunologic: PD, pharmacology
Enzyme Induction: DE, drug effects
Enzyme Inhibitors: PD, pharmacology
*Immune Tolerance: DE, drug effects
Immunosuppressive Agents: AD, administration & dosage
Immunosuppressive Agents: PD, pharmacology
Interferon Type II: GE, genetics
*Interferon Type II: ME, metabolism
Interleukin-12: AD, administration & dosage
***Interleukin-12: PD, pharmacology**
Lymphocyte Transformation: DE, drug effects
Mice
Mice, Inbred A
Mice, Inbred C57BL
Mice, Knockout
Nitric Oxide: IM, immunology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
*Nitric-Oxide Synthase: BI, biosynthesis
Nitric-Oxide Synthase: GE, genetics
NG-Nitroarginine Methyl Ester: PD, pharmacology
Recombinant Proteins: AD, administration & dosage
Recombinant Proteins: PD, pharmacology
T-Lymphocytes: DE, drug effects
T-Lymphocytes: IM, immunology
Vaccines: AD, administration & dosage

L12 ANSWER 11 OF 23 MEDLINE
AN 1998393445 MEDLINE
DN 98393445
TI Vasoactive intestinal peptide inhibits IL-12 and nitric oxide production in murine macrophages.
AU Xin Z; Sriram S
CS Vanderbilt University Medical Center, Nashville, TN, USA.
SO JOURNAL OF NEUROIMMUNOLOGY, (1998 Aug 14) 89 (1-2) 206-12.
Journal code: HSO. ISSN: 0165-5728.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 199811
EW 19981102
AB Vasoactive intestinal peptide (VIP) is a naturally occurring neuropeptide widely distributed in the nervous system. In this study, we investigated the effect of VIP on IL-12, TNF alpha and nitric oxide (NO) production in macrophages following activation with lipopolysaccharide (LPS) or superantigens. In vitro studies show that at physiologic concentrations, VIP inhibited IL-12 and NO but not TNF alpha production in macrophages which were stimulated with LPS or superantigens. The inhibitory effect of VIP on IL-12 production appeared to be cAMP mediated since other cAMP inducing agents were also potent in inhibiting IL-12 production. Since IL-12 plays a critical role in T cell function, we suggest that naturally occurring neural hormones can regulate the type and direction of the immune response.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
Cyclic AMP: ME, metabolism
Forskolin: PD, pharmacology
Interleukin-12: AI, antagonists & inhibitors
***Interleukin-12: BI, biosynthesis**
Lipopolysaccharides: PD, pharmacology
Macrophages, Peritoneal: DE, drug effects
Macrophages, Peritoneal: IM, immunology
*Macrophages, Peritoneal: ME, metabolism
Mice
Mice, Inbred Strains
Mitogens: PD, pharmacology
Neuropeptides: PD, pharmacology
Nitric Oxide: AI, antagonists & inhibitors
*Nitric Oxide: BI, biosynthesis
Superantigens: PD, pharmacology
Thioglycolates: PD, pharmacology
Tumor Necrosis Factor: BI, biosynthesis
Vasoactive Intestinal Peptide: IM, immunology
*Vasoactive Intestinal Peptide: PD, pharmacology
8-Bromo Cyclic Adenosine Monophosphate: PD, pharmacology

L12 ANSWER 12 OF 23 MEDLINE
AN 1998208280 MEDLINE
DN 98208280
TI Alteration of the cytokine phenotype in an experimental lung granuloma model by inhibiting nitric oxide.
AU Hogaboam C M; Chensue S W; Steinhauser M L; Huffnagle G B; Lukacs N W; Strieter R M; Kunkel S L
CS Department of Pathology, University of Michigan Medical School, Ann Arbor 48109-0602, USA.
NC 1P50HL56402 (NHLBI)
HL31963 (NHLBI)
HL35276 (NHLBI)
+
SO JOURNAL OF IMMUNOLOGY, (1997 Dec 1) 159 (11) 5585-93.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199806

AB Pulmonary granulomatous inflammation modulated by IFN-gamma and IL-12 is also associated with augmented inducible nitric oxide synthase (NOS II). To address the role of increased nitric oxide synthesis in this model, mice received daily i.p. injections of NG-nitro-L-arginine-methyl ester (L-NAME; 8 mg/kg) during both the 2-wk immunization period with purified protein-derivative (PPD) and the subsequent lung challenge with PPD-coated Sepharose beads. Other groups of animals received saline, L-NAME or NG-nitro-D-arginine-methyl ester (D-NAME; 8 mg/kg) during the pulmonary embolization period and not the PPD sensitization period. On day 4 post-PPD bead challenge, PCR analysis of the whole lung revealed that NOS II expression appeared to be similar in both of the L-NAME treatment protocols. L-NAME-treated mice in both dosing protocols had lung lesions that were significantly larger than granuloma lesions measured in mice that received saline or D-NAME. The enlarged lesions from L-NAME-treated mice contained markedly greater numbers of neutrophils and eosinophils. Equivalent numbers of PPD-activated dispersed cells from whole lungs of L-NAME-treated mice produced significantly higher levels of IL-4 and IL-10 and smaller amounts of IL-12 and IFN-gamma compared with similar lung cultures derived from control or D-NAME-treated mice. Levels of C-C chemokines such as monocyte chemoattractant protein-1 (MCP-1), C10, and macrophage inflammatory protein-1alpha (MIP-1alpha) were also significantly elevated in lung cultures from L-NAME-treated mice compared with controls. Thus, nitric oxide regulates the size and cellular composition of the Th1-type lung granuloma, possibly through its effects on the cytokine and chemokine profile associated with this lesion.

CT Check Tags: Animal; Female; Support, U.S. Gov't, P.H.S.
*Cytokines: ME, metabolism
Eosinophils: IM, immunology
*Granuloma, Respiratory Tract: IM, immunology
Interferon Type II: ME, metabolism
Interleukin-10: ME, metabolism
Interleukin-12: ME, metabolism
Interleukin-4: ME, metabolism
Lung: EN, enzymology
*Lung Diseases: IM, immunology
Mice
Mice, Inbred CBA
Neutrophils: IM, immunology
Nitric Oxide: AI, antagonists & inhibitors
Nitric Oxide: BI, biosynthesis
*Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: ME, metabolism
NG-Nitroarginine Methyl Ester: PD, pharmacology
*Th1 Cells
Tuberculin: PD, pharmacology
Tumor Necrosis Factor: ME, metabolism

L12 ANSWER 13 OF 23 MEDLINE
AN 1998180349 MEDLINE
DN 98180349
TI Suppression of IL-12 production by phosphodiesterase inhibition in murine endotoxemia is IL-10 independent.
AU Hasko G; Szabo C; Nemeth Z H; Salzman A L; Vizi E S
CS Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest.

SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1998 Feb) 28 (2) 468-72.
Journal code: EN5. ISSN: 0014-2980.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199806
AB Phosphodiesterase (PDE) inhibitors are potent regulators of various immune processes. Immune cells contain type IV and type III PDE. Here we studied in mice the effects of rolipram, a selective PDE IV inhibitor, and amrinone, a selective PDE III blocker, on plasma levels of IL-12 (p70), IFN-gamma, IL-1, TNF-alpha, and nitric oxide (NO) induced by intraperitoneal injection of Escherichia coli lipopolysaccharide (LPS) (80 mg/kg). Pretreatment of BALB/c mice with both rolipram (1-25 mg/kg) and amrinone (10-100 mg/kg) decreased plasma IL-12 levels in a dose-dependent manner. Similarly, LPS-elicited plasma IFN-gamma concentrations were suppressed by both rolipram and amrinone. However, LPS-induced plasma IL-1alpha levels were not affected by either of these compounds. In addition, rolipram inhibited IL-12, IFN-gamma, TNF-alpha and nitrite/nitrate (breakdown products of NO) production in C57BL/6 IL-10(+/+) mice as well as in their IL-10-deficient counterparts (C57BL/6 IL-10(-/-)). Our results suggest that rolipram and amrinone decrease the immune activation in endotoxemia through inhibition of the production of pro-inflammatory mediators IL-12, IFN-gamma, TNF-alpha and NO. These effects are not the consequences of the increase in IL-10 production by PDE inhibition.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Amrinone: AD, administration & dosage
*Endotoxemia: EN, enzymology
*Endotoxemia: IM, immunology
Injections, Intraperitoneal
Interferon Type II: BI, biosynthesis
Interferon Type II: BL, blood
Interleukin-10: BI, biosynthesis
Interleukin-10: DF, deficiency
*Interleukin-10: PH, physiology
***Interleukin-12: AI, antagonists & inhibitors**
***Interleukin-12: BI, biosynthesis**
Interleukin-12: BL, blood
Lipopolysaccharides: AD, administration & dosage
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Mice, Knockout
Nitric Oxide: AI, antagonists & inhibitors
Pyrrolidinones: AD, administration & dosage
Tumor Necrosis Factor: AI, antagonists & inhibitors
*3',5'-Cyclic-Nucleotide Phosphodiesterase: AI, antagonists & inhibitors

L12 ANSWER 14 OF 23 MEDLINE
AN 97270463 MEDLINE
DN 97270463
TI Role of interleukin-10 in regulation of T-cell-dependent and T-cell-independent mechanisms of resistance to Toxoplasma gondii.
AU Neyer L E; Grunig G; Fort M; Remington J S; Rennick D; Hunter C A

CS Department of Immunology and Infectious Diseases, Research Institute, Palo
Alto Medical Foundation, California 94301, USA.
NC AI35956 (NIAID)
SO INFECTION AND IMMUNITY, (1997 May) 65 (5) 1675-82.
Journal code: GO7. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199707
EW 19970703
AB Interleukin-10 (IL-10) is a cytokine which can inhibit T-cell and natural killer (NK) cell functions associated with cell-mediated immunity to intracellular infections. The production of IL-10 by mice infected with Toxoplasma gondii has been implicated in the suppression of lymphocyte proliferation observed during acute toxoplasmosis, as well as susceptibility to infection with this parasite. We have used C57BL/6 mice which lack a functional IL-10 gene (IL-10(-/-) mice) to investigate the role of IL-10 in acute toxoplasmosis. Intraperitoneal infection of IL-10(-/-) mice with T. gondii resulted in 100% mortality by day 13, whereas wild-type C57BL/6 (WT) mice survived acute infection. IL-10(-/-) mice infected with T. gondii had significantly higher serum levels of IL-12 and gamma interferon (IFN-gamma) than WT mice. Early mortality of infected IL-10(-/-) mice was prevented by treatment with IL-10 and significantly delayed by neutralizing antibodies to IL-12 and IFN-gamma. Further studies revealed that SCID/IL-10(-/-) mice infected with T. gondii had delayed time to death compared to IL-10(-/-) mice, indicating that lymphocytes contributed to death of IL-10(-/-) mice. In addition, infected SCID/IL-10(-/-) mice survived longer than infected SCID mice. These latter data indicate that in mice lacking lymphocytes, endogenous IL-10 is associated with increased susceptibility to T. gondii. However, the lack of IL-10 does not alter the infection-induced suppression of T cell and NK cell functions. Our experiments reveal that IL-10 is associated with protection or increased susceptibility to infection with T. gondii, depending on whether mice possess lymphocytes, and demonstrate the important roles of IL-12 and IFN-gamma in the early infection-induced mortality observed in the IL-10(-/-) mice.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
omega-N-Methylarginine: PD, pharmacology
Antibodies, Blocking: IM, immunology
Cell Division
Enzyme-Linked Immunosorbent Assay
Flow Cytometry
*Immunity, Natural: GE, genetics
Interferon Type II: BL, blood
Interferon Type II: IM, immunology
Interferon Type II: ME, metabolism
*Interleukin-10: GE, genetics
*Interleukin-10: IM, immunology
Interleukin-10: PD, pharmacology
Interleukin-12: BL, blood

Interleukin-12: IM, immunology
Interleukin-12: ME, metabolism
Killer Cells, Natural: CY, cytology
*Killer Cells, Natural: IM, immunology
Mice
Mice, Inbred C57BL
Mice, Mutant Strains
Mice, SCID
Neutralization Tests
Nitrites: ME, metabolism
T-Lymphocytes: CY, cytology
*T-Lymphocytes: IM, immunology
*Toxoplasmosis, Animal: IM, immunology

L12 ANSWER 15 OF 23 MEDLINE
AN 97258616 MEDLINE
DN 97258616
TI Intracellular antimicrobial activity in the absence of interferon-gamma: effect of interleukin-12 in experimental visceral leishmaniasis in interferon-gamma gene-disrupted mice.
AU Taylor A P; Murray H W
CS Department of Medicine, Cornell University Medical College, New York 10021, USA.
NC AI-16963 (NIAID)
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1997 Apr 7) 185 (7) 1231-9.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199707
EW 19970703
AB Despite permitting uncontrolled intracellular visceral infection for 8 wk,
interferon-gamma (IFN-gamma) gene knockout (GKO) mice infected with Leishmania donovani proceeded to reduce liver parasite burdens by 50% by week 12. This late-developing IFN-gamma-independent antileishmanial mechanism appeared to be dependent largely on endogenous tumor necrosis factor-alpha (TNF-alpha): L. donovani infection induced TNF-alpha mRNA expression in parasitized GKO livers and neutralization of TNF-alpha reversed control at week 12.7 d of treatment of infected GKO mice with interleukin-12 (IL-12) readily induced leishmanicidal activity and also partially restored the near-absent tissue granulomatous response, observations that for the first time expand the antimicrobial repertoire of IL-12 to include IFN-gamma-independent effects. The action of IL-12 against L. donovani was TNF-alpha dependent and required the activity of inducible nitric oxide synthase. These results point to the presence of an
IFN-gamma-independent antimicrobial mechanism, mediated by TNF-alpha, which remains quiescent until activated late in the course of experimental
visceral leishmaniasis. However, as judged by the effect of exogenous IL-12 this quiescent mechanism can readily be induced to rapidly yield enhanced intracellular antimicrobial activity.
CT Check Tags: Animal; Female; Male; Support, U.S. Gov't, P.H.S.
Drug Interactions
Enzyme Inhibitors

Gene Expression
Granuloma: PS, parasitology
Guanidines: PD, pharmacology
*Interferon Type II: DF, deficiency
Interferon Type II: GE, genetics
***Interleukin-12: PD, pharmacology**
*Leishmaniasis, Visceral: IM, immunology
Liver: EN, enzymology
Liver: PS, parasitology
Mice
Mice, Inbred C57BL
Mice, Knockout
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: BI, biosynthesis
Nitric-Oxide Synthase: GE, genetics
RNA, Messenger: AN, analysis
Tumor Necrosis Factor: BI, biosynthesis
Tumor Necrosis Factor: GE, genetics

L12 ANSWER 16 OF 23 MEDLINE
AN 97176660 MEDLINE
DN 97176660
TI Neospora caninum: role for immune cytokines in host immunity.
AU Khan I A; Schwartzman J D; Fonseka S; Kasper L H
CS Department of Medicine, Dartmouth Medical School, Hanover, New Hampshire 03755, USA.
SO EXPERIMENTAL PARASITOLOGY, (1997 Jan) 85 (1) 24-34.
Journal code: EQP. ISSN: 0014-4894.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199705
EW 19970501
AB Neospora caninum is a coccidial protozoan parasite that infects a large range of mammals including dogs, cats, mice, and cattle. Morphologically, N. caninum appears indistinguishable from Toxoplasma gondii, although they are genetically distinct. To date there have been no reported cases of this infection in humans, although nonhuman primates may be susceptible to infection. Inbred A/J mice develop no clinical and little histologic evidence of infection in spite of a high-dose inoculum of N. caninum. Splenocytes obtained from infected mice proliferate in vitro in response to both N. caninum and T. gondii-soluble antigen. A transient state of T cell hyporesponsiveness to parasite antigen and mitogen was observed at Day 7 p.i. This downregulatory response could be partially reversed by the addition of the nitric oxide antagonist LNMMA, but not antibody to IL-10. Mice infected with N. caninum produce significant quantities of IL-12 and IFN gamma, most evident shortly after infection. In vivo, antibody to IL-12 is able to neutralize immune resistance to the parasite. Moreover, in vivo depletion of IFN gamma with antibody renders the mice susceptible to infection. These observations suggest that N. caninum induces a T cell immune response in the infected host that is at least partially mediated by IL-12 and IFN gamma.
CT Check Tags: Animal; Female; Human

omega-N-Methylarginine: PD, pharmacology
Brain: PA, pathology
Brain: PS, parasitology
*Coccidiosis: IM, immunology
Cytokines: GE, genetics
Cytokines: IM, immunology
*Cytokines: PH, physiology
Disease Susceptibility
Down-Regulation (Physiology): DE, drug effects
Immunity, Cellular
Interferon Type II: GE, genetics
Interferon Type II: IM, immunology
Interferon Type II: PH, physiology
Interleukin-10: GE, genetics
Interleukin-10: IM, immunology
Interleukin-10: PH, physiology
Interleukin-12: GE, genetics
Interleukin-12: IM, immunology
Interleukin-12: PH, physiology
Interleukin-2: GE, genetics
Interleukin-2: IM, immunology
Interleukin-2: PH, physiology
Liver: PA, pathology
Liver: PS, parasitology
Lymphocyte Transformation
Mice
*Neospora: IM, immunology
Nitric Oxide: AI, antagonists & inhibitors
Nitric Oxide: PH, physiology
Pancreas: PA, pathology
Pancreas: PS, parasitology
RNA, Messenger: BI, biosynthesis
Spleen: CY, cytology
Spleen: IM, immunology
Spleen: PS, parasitology
T-Lymphocytes: IM, immunology

L12 ANSWER 17 OF 23 MEDLINE
AN 96295525 MEDLINE
DN 96295525
TI Interferon-gamma-dependent expression of inducible nitric oxide synthase, interleukin-12, and interferon-gamma-inducing factor in macrophages elicited by allografted tumor cells.
AU Sanchez-Bueno A; Verkhusha V; Tanaka Y; Takikawa O; Yoshida R
CS Department of Cell Biology, Osaka Bioscience Institute, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jul 16) 224 (2)
555-63.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199611
AB We have examined the mechanisms of activation of macrophages (Mos) induced
by i.p. allografted Meth A tumor cells (Meth A-Mos) during the rejection

of the cells by C57BL/6 mice. Inducible nitric oxide (NO) synthase (iNOS), interleukin-12 (IL-12), and interferon-gamma (IFN-gamma)-inducing factor (IGIF) were transiently expressed in Meth A-Mos during the rejection. The expression was impaired in mice in which the gene encoding IFN-gamma had been disrupted (IFN-gamma-/-). In vitro studies showed that Meth A-Mos from IFN-gamma +/+ mice induced an apoptotic type of cell death in P815 cells, without cell-to-cell contact, in an NO-dependent manner, whereas Meth A-Mos from IFN-gamma-/- mice could not lyse these cells. The iNOS, IL-12, and IGIF expression was also impaired in bacteria-activated Mos from IFN-gamma-/-mice, indicating that IFN-gamma, but not IGIF, would be the initial signal that leads to the activation of Mos in vivo.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Apoptosis
Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
Base Sequence
Cell Line
Cell Survival: DE, drug effects
Cells, Cultured
*Cytokines: BI, biosynthesis
DNA: AN, analysis
DNA Primers
Enzyme Induction
Enzyme Inhibitors: PD, pharmacology
Fibrosarcoma: EN, enzymology
*Fibrosarcoma: IM, immunology
Gene Expression
Interferon Type II: GE, genetics
*Interferon Type II: PH, physiology
***Interleukin-12: BI, biosynthesis**
Macrophages: EN, enzymology
*Macrophages: IM, immunology
Mice
Mice, Inbred C57BL
Mice, Knockout
Molecular Sequence Data
Mycobacterium bovis: IM, immunology
*Neoplasm Transplantation
Nitric-Oxide Synthase: AI, antagonists & inhibitors
*Nitric-Oxide Synthase: BI, biosynthesis
Polymerase Chain Reaction
Time Factors
Transplantation, Homologous

L12 ANSWER 18 OF 23 MEDLINE
AN 96280727 MEDLINE
DN 96280727
TI Interleukin-12 gene-expression of macrophages is regulated by nitric oxide.
AU Rothe H; Hartmann B; Geerlings P; Kolb H
CS Diabetes Research Institute, Heinrich- Heine University of Dusseldorf, Germany.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Jul 5) 224 (1) 159-63.
Journal code: 9Y8. ISSN: 0006-291X.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199610
AB Interleukin-12 is a heterodimeric cytokine, mainly produced by macrophages. In our present study we demonstrate that interleukin-12 expression is regulated by nitric oxide. Incubation of the macrophage cell line IC 21 with interferon-gamma gave rise to both interleukin-12 p40 mRNA and nitric oxide production. The concurrent addition of the nitric oxide synthase inhibitor N(G)-monomethyl-L-arginine inhibited nitrite production and in parallel completely suppressed interleukin-12 p40 mRNA formation. This indicated that endogenous nitric oxide synthase activity was required for IL-12 p40 gene expression. Exposure of the cells towards the nitric oxide generating compounds nitroprusside or S-nitroso-N-acetyl-penicillamine induced interleukin-12 p40 mRNA. Maximal mRNA levels were induced with nitric oxide donors at 1 microM concentration. We conclude that nitric oxide may exert an autoregulatory and paracrine control of interleukin-12 gene expression.
CT Check Tags: Animal; Support, Non-U.S. Gov't
*Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
Cell Line
Enzyme Inhibitors: PD, pharmacology
Gene Expression Regulation: DE, drug effects
*Gene Expression Regulation: IM, immunology
Interferon-gamma, Recombinant: PD, pharmacology
***Interleukin-12: BI, biosynthesis**
Macrophage Activation
Macrophages: DE, drug effects
*Macrophages: IM, immunology
Mice
*Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitroprusside: PD, pharmacology
Penicillamine: AA, analogs & derivatives
Penicillamine: PD, pharmacology
Rats
RNA, Messenger: BI, biosynthesis
Transcription, Genetic: DE, drug effects

L12 ANSWER 19 OF 23 MEDLINE
AN 96197369 MEDLINE
DN 96197369
TI Effects of N(g)-methyl-L-arginine, an inhibitor of nitric oxide synthesis, on interleukin-2-induced capillary leakage and antitumor responses in healthy and tumor-bearing mice.
AU Orucevic A; Lala P K
CS Department of Anatomy, University of Western Ontario, Canada.
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1996 Jan) 42 (1) 38-46.
Journal code: CN3. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals; Cancer Journals
EM 199608
AB We tested whether treatment with an inhibitor of nitric oxide synthesis (N{g}-methyl-L-arginine, MeArg) can ameliorate interleukin-2(IL-2)-therapy-induced capillary leak syndrome in healthy or tumor-bearing mice without compromising the antitumor effects of IL-2 therapy. Healthy or C3-L5-mammary-adenocarcinoma-bearing C3H/HeJ mice were treated with one or two rounds of various doses of IL-2 (ten injections, i. p., every 8 h) or MeArg (ten injections s. c., every 8 h) or their combination. In an additional experiment, MeArg was given chronically in the drinking water, rather than s. c. to healthy mice subjected to one round of therapy as above. Mice were killed 1 h after their last IL-2 injection to measure the water content of the lungs and pleural cavities (markers of capillary leakage), NO production (given by NO2- and NO3- levels in the serum and pleural effusion), as well as the effect of therapies on the primary tumor size and number of spontaneous lung metastatic nodules. Results revealed that all doses of IL-2 (7500-35000 Cetus U/injection), as well as both rounds of IL-2 therapy, caused capillary leakage. However, no pleural effusion was seen after the second round in any of the IL-2-treated groups. MeArg therapy, given subcutaneously (5-20 mgkg(-1) injection(-1) in healthy and 20 mgkg(-1) injection(-1) in tumor-bearing mice), did not ameliorate IL-2-induced capillary leakage in either group of mice, and did not compromise antitumor effects of IL-2. However, subcutaneous MeArg therapy alone reduced the growth of the primary tumors, the occurrence of lung metastases and the amount of tumor-induced pulmonary edema. When MeArg therapy was given orally (1 mg/ml drinking water), a substantial drop in NO production, as well as reduction in capillary leakage was noted in IL-2-treated healthy mice. These findings suggest that NO inhibitors could be a valuable adjunct to IL-2 therapy of cancer and infectious diseases.
CT Check Tags: Animal; Female; Support, Non-U.S. Gov't
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: ME, metabolism
Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: PK, pharmacokinetics
*Antineoplastic Agents: TO, toxicity
*Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
*Capillary Permeability: DE, drug effects
Cell Division: DE, drug effects
Dose-Response Relationship, Drug
Drug Interactions
*Enzyme Inhibitors: PD, pharmacology
Interleukin-12: PD, pharmacology
***Interleukin-12: TO, toxicity**
*Mammary Neoplasms, Experimental: DT, drug therapy
Mammary Neoplasms, Experimental: ME, metabolism
Mice
Mice, Inbred C3H
Nitric Oxide: AI, antagonists & inhibitors

*Nitric Oxide: BI, biosynthesis
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Pleural Effusion: CI, chemically induced
Pulmonary Edema: CI, chemically induced

L12 ANSWER 20 OF 23 MEDLINE
AN 96180196 MEDLINE
DN 96180196
TI Bacterial superantigen-induced human lymphocyte responses are nitric oxide dependent and mediated by IL-12 and IFN-gamma.
AU Sriskandan S; Evans T J; Cohen J
CS Department of Infectious Diseases and Bacteriology, Royal Postgraduate Medical School, Hammersmith Hospital, London, United Kingdom.
SO JOURNAL OF IMMUNOLOGY, (1996 Apr 1) 156 (7) 2430-5.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199611
AB Bacterial superantigens cause marked proliferation of T cells and release of lymphokines. Nitric oxide, derived from the conversion of L-arginine to L-citrulline, inhibits this activation in murine cells. We have now investigated the roles of IL-12, IFN-gamma, lymphotoxin-alpha, and nitric oxide during superantigen-induced human lymphocyte activation. Lymphocyte activation was determined by measurement of proliferative responses and lymphokine release. Both toxic shock syndrome toxin-1 from Staphylococcus aureus and recombinant streptococcal pyrogenic exotoxin A induced proliferation and production of IFN-gamma, lymphotoxin-alpha, and IL-12 by human mononuclear cells in a time-dependent fashion. The release of IFN-gamma was abrogated by a neutralizing Ab to IL-12, but lymphocyte proliferative responses were unaffected. A neutralizing Ab to IFN-gamma prevented the release of lymphotoxin-alpha, but did not affect proliferation. The neutralization of lymphotoxin-alpha using two different Abs did not affect IFN-gamma release or proliferation. In contrast to previous findings in mice, the arginine analogue, NG-monomethyl-L-arginine, significantly inhibited both proliferation and lymphokine release by superantigen-stimulated human cells. Thus, the release of lymphotoxin-alpha by lymphocytes following superantigen stimulation is dependent upon the presence of IFN-gamma; the IFN-gamma response is in turn under the control of IL-12. There is no evidence that nitric oxide plays an inhibitory role during superantigen-mediated human lymphocyte activation. Indeed, arginine is a prerequisite for such activation.
CT Check Tags: Animal; Human; In Vitro
Antibodies, Monoclonal: PD, pharmacology
Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
Base Sequence
DNA Primers: GE, genetics
Enzyme Inhibitors: PD, pharmacology
Exotoxins: AD, administration & dosage
Exotoxins: GE, genetics
Interferon Type II: AI, antagonists & inhibitors

*Interferon Type II: BI, biosynthesis
Interleukin-12: AI, antagonists & inhibitors
***Interleukin-12: BI, biosynthesis**
Kinetics
Lymphocyte Transformation: DE, drug effects
*Lymphocyte Transformation: PH, physiology
Lymphocytes: DE, drug effects
Lymphocytes: IM, immunology
Lymphocytes: ME, metabolism
Lymphotoxin: AI, antagonists & inhibitors
Lymphotoxin: BI, biosynthesis
Mice
Molecular Sequence Data
Neutralization Tests
*Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitrites: ME, metabolism
*Superantigens: AD, administration & dosage
Superantigens: GE, genetics

L12 ANSWER 21 OF 23 MEDLINE
AN 96132990 MEDLINE
DN 96132990
TI Production of nitric oxide (NO) is not essential for protection against acute Toxoplasma gondii infection in IRF-1-/- mice.
AU Khan I A; Matsuura T; Fonseka S; Kasper L H
CS Department of Medicine, Dartmouth Medical School, Hanover, NH 03755, USA.
NC AI19613 (NIAID)
AI35956 (NIAID)
AI33325 (NIAID)
SO JOURNAL OF IMMUNOLOGY, (1996 Jan 15) 156 (2) 636-43.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199604
AB Production of nitric oxide (NO) by macrophages is important for the killing of intracellular pathogens. IFN-gamma and LPS stimulate NO production by transcriptional up-regulation of inducible nitric oxide synthetase (iNOS). In the present study we used mice with a targeted disruption of the IFN regulatory factor-1 gene (IRF-1-/-) to investigate the importance of NO in the host immune response against Toxoplasma gondii, a major cause of infection in newborns and those with AIDS. IRF-1-/- mice were more susceptible to acute Toxoplasma infection, and treatment with either exogenous IFN-gamma or in vivo neutralization of endogenous IFN-gamma had little effect on their susceptibility to infection. However, administration of exogenous IL-12 was able to prolong survival even when IFN-gamma was depleted. An in vivo depletion study suggested that the mechanism of this protective response is mediated in part by CD4+ T cells. The administration of IL-12 could not overcome the inhibition of lymphoproliferative response in T. gondii-infected mice and treatment with N-monomethyl-L-arginine (L-NMMA), a nitric oxide synthase (iNOS) antagonist in vitro was unable to reverse the immunosuppression. In response to Toxoplasma infection, splenocytes from IRF-1-/- mice exhibited

increased production of IL-10 as well as a 30-fold increase in its message expression. These studies indicate that NO may not be essential for host immunity to the parasite, and moreover that IL-12 appears to induce an IFN-gamma-independent mechanism of protection against this opportunistic pathogen.

CT Check Tags: Animal; Female; Support, U.S. Gov't, P.H.S.
Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
Biological Response Modifiers: TU, therapeutic use
CD4-Positive T-Lymphocytes
Disease Susceptibility: GE, genetics
DNA-Binding Proteins: GE, genetics
*DNA-Binding Proteins: PH, physiology
Interferon Type II: PD, pharmacology
Interleukin-10: PD, pharmacology
Interleukin-12: PD, pharmacology
***Interleukin-12: TU, therapeutic use**
Lymphocyte Depletion
Lymphocyte Transformation
Mice
Mice, Inbred C57BL
Mice, Knockout
*Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Phosphoproteins: GE, genetics
*Phosphoproteins: PH, physiology
T-Lymphocyte Subsets: DE, drug effects
*T-Lymphocyte Subsets: IM, immunology
*Toxoplasma: PH, physiology
*Toxoplasmosis, Animal: PC, prevention & control
Toxoplasmosis, Animal: TH, therapy
Transforming Growth Factor beta: PD, pharmacology

L12 ANSWER 22 OF 23 MEDLINE
AN 95332736 MEDLINE
DN 95332736
TI IL-12 prevents mortality in mice infected with Histoplasma capsulatum through induction of IFN-gamma.
AU Zhou P; Sieve M C; Bennett J; Kwon-Chung K J; Tewari R P; Gazzinelli R T; Sher A; Seder R A
CS Lymphokine Regulation Unit, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA..
SO JOURNAL OF IMMUNOLOGY, (1995 Jul 15) 155 (2) 785-95.
Journal code: IFB. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199510
AB Histoplasma capsulatum is a pathogenic fungus found in discrete geographic locations throughout the world. The fungus invades the reticuloendothelial organs such as the spleen and liver of immunocompetent hosts where it is usually controlled. However, in individuals with immune deficiency, histoplasmosis is a severe and potentially fatal disease. Resistance to

this infection is due primarily to a cellular immune response mediated by T cells and macrophages. Moreover, IFN-gamma is critical in activating macrophages to kill the organism. Herein we study the regulation of cytokine induction in mice infected with H. capsulatum and the effects of IL-12 in the course of infection. Mice infected with H. capsulatum and treated with neutralizing Abs to IFN-gamma, TNF-alpha, or IL-12 experienced accelerated mortality, indicating that endogenous production of these cytokines plays an important role in response to infection. In contrast, mice treated with IL-12 or a neutralizing Ab to IL-4 at the initiation of infection had substantially diminished mortality. Moreover, mice infected and treated with IL-12 show a two- to threefold increase in the amount of IFN-gamma following in vitro stimulation with specific H. capsulatum Ag compared with the control infected mice. The protective effect of IL-12 could be abrogated if a neutralizing Ab to IFN-gamma was given at the same time, demonstrating that the role of IL-12 in protection was mediated by IFN-gamma. Additionally, infected mice treated with IL-12 had a severalfold decrease in the colony counts of H. capsulatum in spleen cells after 5 days of infection as compared with control animals. Lastly, spleen cells from infected animals treated with IL-12 showed a striking decrease in their proliferative response to mitogen or H. capsulatum Ag. Responses could be restored by adding inhibitors of IFN-gamma or of nitric oxide to the in vitro cultures. The above observations suggest that IL-12 may be useful in immunologic intervention against this opportunistic pathogen.

CT Check Tags: Animal; Female
Antibodies: IM, immunology
Antibody Formation
Antigens, Fungal: PD, pharmacology
Binding, Competitive: IM, immunology
Cell Division: IM, immunology
Histoplasmosis: IM, immunology
*Histoplasmosis: MO, mortality
*Histoplasmosis: TH, therapy
Immunity, Cellular
Interferon Type II: AI, antagonists & inhibitors
*Interferon Type II: BI, biosynthesis
Interferon Type II: PH, physiology
Interleukin-12: GE, genetics
***Interleukin-12: PH, physiology**
***Interleukin-12: TU, therapeutic use**
Interleukin-4: BI, biosynthesis
Lymphocyte Transformation: IM, immunology
Mice
Mice, Inbred C57BL
Mitogens: PD, pharmacology
Nitric Oxide: AI, antagonists & inhibitors
RNA, Messenger: BI, biosynthesis
Spleen: CY, cytology
Tumor Necrosis Factor: AI, antagonists & inhibitors
Tumor Necrosis Factor: BI, biosynthesis
Tumor Necrosis Factor: PH, physiology

L12 ANSWER 23 OF 23 MEDLINE
AN 95024182 MEDLINE

DN 95024182
TI Interleukin 12 induction of interferon gamma-dependent protection against malaria.
AU Sedegah M; Finkelman F; Hoffman S L
CS Malaria Program, Naval Medical Research Institute, Bethesda, MD 20889-5607.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1994 Oct 25) 91 (22) 10700-2.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199501
AB Intraperitoneal injection of recombinant Interleukin 12 (rIL-12) at 30 ng/day for 5 days beginning 1 to 2 days before sporozoite challenge or administration of a single dose of 150 ng of rIL-122 days before challenge protected 100% of BALB/c mice against challenge with 10(2) Plasmodium yoelii sporozoites. rIL-12-induced protection was eliminated in all mice by administration of a monoclonal antibody against interferon gamma and in 50% of mice by administration of NG-monomethyl-L-arginine, a competitive inhibitor of nitric oxide synthase. rIL-12 protected BALB/c mice treated with cytotoxic anti-CD4 and anti-CD8 monoclonal antibodies, as well as T-cell- and B-cell-deficient severe combined immunodeficiency mice. These data suggest that rIL-12 stimulates non-B, non-T cells to produce interferon gamma that kills intrahepatic parasites by stimulating nitric oxide production. If rIL-12 proves to be well tolerated by humans, our findings support consideration of rIL-12 as an immunoprophylactic against malaria.
CT Check Tags: Animal; Female; Support, U.S. Gov't, Non-P.H.S.
Antibodies, Monoclonal
Arginine: AA, analogs & derivatives
Arginine: PD, pharmacology
*B-Lymphocytes: IM, immunology
CD4-Positive T-Lymphocytes: IM, immunology
CD8-Positive T-Lymphocytes: IM, immunology
Interferon Type II: IM, immunology
*Interferon Type II: PH, physiology
***Interleukin-12: PD, pharmacology**
Killer Cells, Natural: IM, immunology
Lymphocyte Depletion
*Malaria: IM, immunology
Malaria: PC, prevention & control
Mice
Mice, Inbred BALB C
Mice, SCID
Nitric Oxide: AI, antagonists & inhibitors
Nitric Oxide: BI, biosynthesis
*Plasmodium yoelii
Rats
Recombinant Proteins: PD, pharmacology
*T-Lymphocytes: IM, immunology

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               DEL HIS Y
L1          4244 S INTERLEUKIN 12/CT
L2          2057 S L1/MAJ
L3         28006 S NITRIC OXIDE/CT
L4          3789 S NITRIC OXIDE SYNTHASE INHIBITOR/CT
L5         12926 S NITRIC OXIDE SYNTHASE/CT
L6            55 S L2 AND L3
L7             3 S L4 AND L2
L8            38 S L5 AND L2
L9            80 S L8 OR L6
L10       789071 S INHIBIT?
L11       184152 S ANTAGONIS?
L12       892752 S L11 OR L10
L13           34 S L12 AND L9
                 E IMMUNOSTIMULANTS/CT
                 E E5+ALL
                 E IMMUNOSTIUMLANTS/CT
                 E E1+ALL
L14         7786 S IMMUNOSTIMULATION/CT
L15            4 S L14 AND L9
                 E ADJUVANTS/CT
                 E E5+ALL
                 E IMMUNOLOGICAL ADJUVANT/CT
                 E E3+ALL
L16         1181 S IMMUNOLOGICAL ADJUVANT/CT
L17            0 S L9 AND L16
L18        89833 S VACCIN?
L19            6 S L9 AND L18
L20            0 S L9 AND SCAVENG?
L21           13 S L19 OR L15 OR L7
L22           27 S L13 NOT L21

     FILE 'EMBASE' ENTERED AT 11:38:48 ON 22 FEB 2001

=> d bib ab ct l21 1-13;d bib ab ct l22 1-27


L21  ANSWER 1 OF 13  EMBASE  COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN   2000233239  EMBASE
TI   Interleukin-12 (IL-12) enhancement of the cellular immune response
against
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human immunodeficiency virus type 1 Env antigen in a DNA prime/ **vaccinia** virus boost **vaccine** regimen is time and dose dependent: Suppressive effects of IL-12 boost are mediated by nitric oxide.

AU Gherardi M.M.; Ramirez J.C.; Esteban M.
CS M. Esteban, Centro Nacional Biotecnologia, (CSIC), Campus Cantoblanco, 28049 Madrid, Spain. mesteban@cnb.uam.es

SO Journal of Virology, (2000) 74/14 (6278-6286).
Refs: 59
ISSN: 0022-538X CODEN: JOVIAM
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English

AB We previously demonstrated that codelivery of interleukin-12 (IL-12) with the human immunodeficiency virus type 1 (HIV-1) Env antigen from a recombinant **vaccinia** virus (rVV) can enhance the specific anti-Env cell- mediated immune (CMI) response. In the present study, we have investigated the effects of IL-12 in mice when it is expressed in a DNA prime/VV boost **vaccine** regimen. The delivery of IL-12 and Env product during priming with a DNA vector, followed by a booster with VV expressing the Env gene (rVVenv), was found to trigger the optimal CMI response compared with other immunization schedules studied. Significantly, if IL-12 is also delivered as a booster from the viral vector, an impairment of the effects of IL-12 was observed involving nitric oxide (NO), since it was overcome by specific inhibitors of inducible NO synthase. NO caused transient immunosuppression rather than impairment of viral replication. Moreover, at certain viral doses, coadministration of the NO inhibitor during the booster resulted in IL-12-mediated enhancement of the specific CD8+ T-cell response. In addition, the dose of the IL-12-encoding plasmid (pIL-12) and the route of administration of both vectors were relevant factors for optimal CMI responses. Maximal numbers of Env-specific CD8+ gamma interferon-secreting cells were obtained when 50 .mu.g of pIL-12 was administered intramuscularly at priming, followed by an intravenous rVVenv boost. Our results demonstrate, in a murine model, critical parameters affecting the success of **vaccination** schedules based on a combination of DNA and VV vectors in conjunction with immunomodulators.

CT Medical Descriptors:
*cellular immunity
*Human immunodeficiency virus 1
*immune response
Vaccinia virus
virus recombinant
envelope gene
virus replication
cytokine release
immunization
virus vector
dose response
immunomodulation
human
nonhuman

mouse
animal experiment
human cell
animal cell
article
priority journal
Drug Descriptors:
***interleukin 12**
*virus antigen: EC, endogenous compound
*virus envelope protein: EC, endogenous compound
***nitric oxide**
***nitric oxide synthase**
*virus DNA: EC, endogenous compound

L21 ANSWER 2 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000009208 EMBASE
TI IL-4 and IL-10 antagonize IL-12-mediated protection against acute **vaccinia** virus infection with a limited role of IFN-.gamma. and nitric oxide synthetase 2.
AU Van den Broek M.; Bachmann M.F.; Kohler G.; Barner M.; Escher R.; Zinkernagel R.; Kopf M.
CS Dr. M. Kopf, Basel Institute for Immunology, Grenzacherstr. 487, 4005 Basel, Switzerland. kopf@bii.ch
SO Journal of Immunology, (1 Jan 2000) 164/1 (371-378).
Refs: 89
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Resistance or susceptibility to most infectious diseases is strongly determined by the balance of type 1 vs type 2 cytokines produced during infection. However, for viruses, this scheme may be applicable only to infections with some cytopathic viruses, where IFN-.gamma. is considered as mandatory for host defense with little if any participation of type 2 responses. We studied the role of signature Th1 (IL-12, IFN-.gamma.) and Th2 (IL- 4, IL-10) cytokines for immune responses against **vaccinia** virus (VV). IL-12(- /-) mice were far more susceptible than IFN-.gamma.(-/-) mice, and primary CTL responses against VV were absent in IL-12(-/-) mice but remained intact in IFN-.gamma.(-/-) mice! Both CD4+ and CD8+ T cells from IL-12(-/-) mice were unimpaired in IFN-.gamma. production, although CD4+ T cells showed elevated Th2 cytokine responses. Virus replication was impaired in IL-4(-/-) mice and, even more strikingly, in IL-10(-/-) mice, which both produced elevated levels of the proinflammatory cytokines IL-1.alpha. and IL-6. Thus, IL-4 produced by Th2 cells and IL-10 produced by Th2 cells and probably also by macrophages counteract efficient anti-viral host defense. Surprisingly, NO production, which is considered as a major type 1 effector pathway inhibited by type 2 cytokines, appears to play a limited role against VV, because NO sythetase

2- deficient mice did not show increased viral replication. Thus, our results identify a new role for IL-12 in defense beyond the induction of IFN-.gamma. and show that IL-4 and IL-10 modulate host protective responses to VV.

CT Medical Descriptors:
***vaccinia**
*immune response
host resistance
infection sensitivity
cytokine production
T lymphocyte
virus replication
host susceptibility
immunoregulation
regulatory mechanism
nonhuman
mouse
animal experiment
animal model
animal cell
article
priority journal
Drug Descriptors:
*interleukin 10: EC, endogenous compound
*interleukin 4: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
*gamma interferon: EC, endogenous compound
***nitric oxide synthase**
interleukin 1: EC, endogenous compound
interleukin 6: EC, endogenous compound
nitric oxide

L21 ANSWER 3 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999389037 EMBASE
TI Vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide inhibit interleukin-12 transcription by regulating nuclear factor .kappa.B and Ets activation.
AU Delgado M.; Ganea D.
CS D. Ganea, Rutgers Univ., Dept. Biological Sciences, 101 Warren St., Newark, NJ 07102, United States. dganea@andromeda.rutgers.edu
SO Journal of Biological Chemistry, (5 Nov 1999) 274/45 (31930-31940). Refs: 70
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB The vasoactive intestinal peptide (VIP) and the structurally related neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) act as 'macrophage-deactivating factors'. We showed previously that VIP and PACAP inhibit the production of macrophage-derived tumor necrosis factor-.alpha., interleukin (IL)-6, nitric oxide, and IL-12. This study examines the molecular mechanisms involved in the VIP/PACAP inhibition of IL-12 production. VIP and PACAP inhibit IL-12 (p40) gene expression by affecting both NF-.kappa.B binding and the composition of the Ets-2

binding complex. Both neuropeptides prevent the activation-induced nuclear translocation of the NF- .kappa.B components p65 and c-Rel by inhibiting the reduction in cytoplasmic I.kappa.B.alpha.. Moreover, VIP and PACAP inhibit the synthesis of the interferon responsive factor-1. The decrease in nuclear interferon responsive factor-1 and c-Rel results in alterations of the Ets-2-binding complex. Two transduction pathways, a cAMP-dependent and a cAMP-independent pathway, are involved in the inhibition of IL-12 gene expression and appear to differentially regulate the transcriptional factors involved. Because IL-12 participates in T cell activation and cytolytic T lymphocyte activity and promotes the differentiation of T helper cells into the Th1 subset, the understanding of the mechanisms that affect IL-12 production in normal and pathological conditions could contribute to immune response-based therapies or **vaccine** designs.

CT Medical Descriptors:
*transcription regulation
regulatory mechanism
cytokine production
molecular dynamics
gene expression
t lymphocyte activation
immune response
nonhuman
mouse
controlled study
animal cell
article
priority journal
Drug Descriptors:
*vasoactive intestinal polypeptide
*hypophysis adenylate cyclase activating polypeptide
***interleukin 12: EC, endogenous compound**
*immunoglobulin enhancer binding protein: EC, endogenous compound
*neuropeptide
synaptotagmin: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
nitric oxide: EC, endogenous compound

L21 ANSWER 4 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999231229 EMBASE
TI Immune-stimulating complexes induce an IL-12-dependent cascade of innate immune responses.
AU Smith R.E.; Donachie A.M.; Grdic D.; Lycke N.; Mowat A.McI.
CS Dr. A.McI. Mowat, Department of Immunology, University of Glasgow, Western Infirmary, Glasgow G11 6NT, United Kingdom. a.m.mowat@clinmed.gla.ac.uk
SO Journal of Immunology, (1 May 1999) 162/9 (5536-5546).
Refs: 46
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English

AB The development of subunit **vaccines** requires the use of adjuvants that act by stimulating components of the innate immune response. Immune- stimulating complexes (ISCOMS) containing the saponin adjuvant Quil A are potential **vaccine** vectors that induce a wide range of Ag-specific responses in vivo encompassing both humoral and CD4 and CD8 cell-mediated immune responses. ISCOMS are active by both parenteral and mucosal routes, but the basis for their adjuvant properties is unknown. Here we have investigated the ability of ISCOMS to recruit and activate innate immune responses as measured in peritoneal exudate cells. The i.p. injection of ISCOMS induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes. Many of the recruited cells had phenotypic evidence of activation and secreted a number of inflammatory mediators, including nitric oxide, reactive oxygen intermediates, IL-1, IL-6, IL-12, and IFN-.gamma.. Of the factors that we investigated further only IL-12 appeared to be essential for the immunogenicity of ISCOMS, as IL-6- and inducible nitric oxide synthase knockout (KO) mice developed normal immune responses to OVA in ISCOMS, whereas these responses were markedly reduced in IL-12KO mice. The recruitment of peritoneal exudate cells following an injection of ISCOMS was impaired in IL-12KO mice, indicating a role for IL-12 in establishing the proinflammatory cascade. Thus, ISCOMS prime Ag-specific immune responses at least in part by activating IL-12-dependent aspects of the innate immune system.

CT Medical Descriptors:
*inflammation
*immune response
antigen specificity
cellular immunity
neutrophil
mast cell
immunogenicity
knockout mouse
immunohistochemistry
flow cytometry
phenotype
nonhuman
female
mouse
animal experiment
animal model
controlled study
animal cell
article
priority journal
Drug Descriptors:
***interleukin 12**
*iscom
quil a
cd4 antigen
cd8 antigen
nitric oxide
interleukin 1
interleukin 6
gamma interferon
nitric oxide synthase

L21 ANSWER 5 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999112591 EMBASE
TI Strategies of protection from nitric oxide toxicity in islet inflammation.
AU Rothe H.; Kolb H.
CS H. Rothe, Diabetes Research Institute, Heinrich-Heine Univ. of Dusseldorf,
Auf'm Hennekamp 65, D-40225 Dusseldorf, Germany
SO Journal of Molecular Medicine, (1999) 77/1 (40-44).
Refs: 51
ISSN: 0946-2716 CODEN: JMLME8
CY Germany
DT Journal; Conference Article
FS 003 Endocrinology
005 General Pathology and Pathological Anatomy
LA English
SL English
AB Nitric oxide is thought to contribute to beta cell destruction during islet inflammation in animal models of type I diabetes. In vitro, inhibition of inducible nitric oxide synthase protects islet cells from the damaging effects of inflammatory cells or cytokines. However, the administration of several inducible nitric oxide synthase inhibitors to prediabetic animals had variable effects on disease progression. An alternative approach is to prevent the lethal consequences of nitric oxide
action at the level of islet cells. We observed that the suppression of poly-(ADP-ribose)-polymerase ensures survival of islet cells exposed to nitric oxide. Cells could also be rendered resistant by the induction of endogenous stress proteins in particular of heat shock protein 70. Nitric oxide is not only a strong cytotoxic agent, but is also able to modulate immune reactions by interfering with Th1/Th2 reactivities. This may occur via induction of the interleukin- 12 antagonist IL-12(p40)2. Development of type I diabetes is known to be correlated with a shift from a Th2 status during benign insulitis to a Th1 status during destructive insulitis. This shift was found dependent on local interleukin-12 gene expression. Indeed, administration of a natural interleukin-12 antagonist suppressed the progression of islet inflammation and concomitant upregulation of the inducible nitric oxide synthase.
CT Medical Descriptors:
*insulin dependent diabetes mellitus
inflammation
pancreas islet beta cell
inflammatory cell
enzyme repression
cell survival
insulitis
gene expression
helper cell
conference paper
Drug Descriptors:
*nitric oxide
*nitric oxide synthase
***nitric oxide synthase inhibitor**
***interleukin 12**
cytokine
nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase

heat shock protein 70

L21 ANSWER 6 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97372660 EMBASE
DN 1997372660
TI Interleukin-12 is critical for induction of nitric oxide-mediated immunosuppression following **vaccination** of mice with attenuated Salmonella typhimurium.
AU Schwacha M.G.; Eisenstein T.K.
CS T.K. Eisenstein, Dept. of Microbiology/Immunology, Temple University School of Medicine, 3400 North Broad St., Philadelphia, PA 19140, United States. tke@astro.ocis.temple.edu
SO Infection and Immunity, (1997) 65/12 (4897-4903).
Refs: 75
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Studies from our laboratory have shown that infection of mice with an attenuated strain of Salmonella typhimurium causes a marked suppression in the capacity of splenocytes to generate an in vitro plaque-forming cell (PFC) response to sheep erythrocytes. The suppression has been shown to be mediated by mature, adherent macrophages (M.PHI.s) and nonadherent, precursor M.PHI.s. Nitric oxide has been identified as the suppressor factor. The present study investigated the role of interleukin-12 (IL-12) in the generation of nitric oxide-mediated immunosuppression in this model. Salmonella inoculation resulted in marked suppression of PFC responses and high levels of nitrite production. When mice were treated with anti-IL-12 prior to inoculation, nitrite levels in splenocyte cultures were reduced by 75% and the suppression of PFC responses was prevented. The nonadherent splenocyte fraction from Salmonella-inoculated mice, which contains precursor M.PHI.s and is weakly immunosuppressive, was treated with IL-12 in vitro. IL-12 augmented the capacity of this fraction to suppress PFC responses by normal splenocytes in a coculture system. Additionally, IL-12 induced nitrite and gamma interferon (IFN-.gamma.) production in a dose-dependent manner. Treatment with anti-IFN-.gamma. blocked nitrite production and suppression, indicating that IFN-.gamma. is an important intermediary in the pathway of IL-12-induced immunosuppression. These results indicate that IL-12 is critical for the induction of nitric oxide-mediated immunosuppression following S. typhimurium inoculation and, through its ability to stimulate IFN-.gamma. production, can induce nitric oxide- producing suppressor M.PHI.s.
CT Medical Descriptors:
*immunosuppressive treatment
*salmonella typhimurium
***vaccination**
animal experiment
article
controlled study
erythrocyte

immunomodulation
inoculation
macrophage function
mouse
nonhuman
priority journal
spleen cell
Drug Descriptors:
***interleukin 12**
nitric oxide

L21 ANSWER 7 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97102136 EMBASE
DN 1997102136
TI Interleukin-12 synthesis is a required step in trehalose dimycolate-induced activation of mouse peritoneal macrophages.
AU Oswald I.P.; Dozois C.M.; Petit J.-F.; Lemaire G.
CS G. Lemaire, URA CNRS 1116, Universite Paris Sud, Batiment 430, 91405 Orsay
Cedex, France
SO Infection and Immunity, (1997) 65/4 (1364-1369).
Refs: 63
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Trehalose dimycolate (TDM), a glycolipid present in the cell wall of Mycobacterium spp., is a powerful immunostimulant. TDM primes murine macrophages (M.phi.) to produce nitric oxide (NO) and to develop antitumoral activity upon activation with low doses of lipopolysaccharide (LPS). In this study, we investigated the ability of TDM to induce interleukin 12 (IL-12) and the role of this cytokine in TDM-induced activation of murine M.phi.. RNA isolated from peritoneal exudate cells (PEC) collected at different times after TDM injection was used to determine IL-12 (p35 and p40 subunits) and gamma interferon (IFN-.gamma.) mRNA levels by semiquantitative reverse transcriptase-PCR. Constitutive expression of IL-12p35 was observed in PEC from untreated as well as from TDM-injected mice. In contrast, expression of the IL-12p40 subunit was almost undetectable in control PEC but was dramatically upregulated in PEC from TDM-injected mice. IL-12p40 expression peaked at 8 h and subsided to baseline levels at 39 h postinjection. TDM was also able to induce IFN-.gamma. expression; however, kinetics of induction of IFN- .gamma. was different from that of IL-12p40. Maximal levels of IFN-.gamma. mRNA were reached by 24 h and did not return to baseline by 4 days. In addition, pretreatment of mice with neutralizing monoclonal antibodies directed against IL-12 (C15.6.7 and C15.1.2) blocked IFN-.gamma. mRNA induction in PEC from TDM- treated mice. We further determined if the induction of IL-12 and/or IFN-.gamma. contributes to the in vivo priming effect of TDM on peritoneal M.phi.. TDM- injected mice were treated in vivo with anti-IL-12 or anti-IFN-.gamma. (XMG.1.6) monoclonal antibodies. TDM-primed M.phi. were then activated in vitro with LPS and tested for their ability

to produce NO and to develop cytostatic activity toward cocultivated
L1210
tumor cells. Priming of M.phi. by TDM was completely blocked by in vivo neutralization of either IL-12 or IFN-.gamma. as demonstrated by an absence of tumoricidal activity and NO production by TDM-elicited M.phi. in the presence of LPS. Taken together our results show that TDM, a defined molecule from M. tuberculosis, induces in vivo production of IL-12. Moreover, synthesis of IL-12 mediates TDM priming of mouse peritoneal M.phi. through IFN- .gamma. induction.

CT Medical Descriptors:
*macrophage activation
*protein synthesis regulation
animal cell
article
bacterial cell wall
female
gene expression regulation
immunoregulation
immunostimulation
interferon production
mouse
mycobacterium
nonhuman
peritoneum macrophage
priority journal
Drug Descriptors:
***interleukin 12**
gamma interferon
messenger rna
nitric oxide
trehalose

L21 ANSWER 8 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97102127 EMBASE
DN 1997102127
TI Expression of cytokines and inducible nitric oxide synthase mRNA in the lungs of mice infected with Cryptococcus neoformans: Effects of interleukin- 12.
AU Kawakami K.; Tohyama M.; Qifeng X.; Saito A.
CS K. Kawakami, First Dept. of Internal Medicine, Faculty of Medicine, University of Ryukyus, 207 Uehara, Nishihara, Okinawa 903-01, Japan
SO Infection and Immunity, (1997) 65/4 (1307-1312).
Refs: 51
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB We have recently established a murine model of pulmonary and disseminated infection with a highly virulent strain of Cryptococcus neoformans and demonstrated that administration of interleukin-12 (IL-12) protected the animals against infection. In this study, we extended these studies by investigating the host defense mechanisms. In particular, we examined the expression of mRNA for helper T-cell 1 (Th1) cytokines (IL-2, lymphotoxin,

and gamma interferon [IFN-.gamma.]), Th2 cytokines (IL-4, -6, and - 10), macrophage-derived cytokines (tumor necrosis factor alpha [TNF-.alpha.], IL- 1.beta., transforming growth factor .beta. [TGF-.beta.], IL-12p40, and IFN-.gamma.-inducing factor [IGIF]), and inducible nitric oxide synthase (iNOS) in the lungs on days 1, 3, 7, and 14 after infection and following treatment with IL-12. There was little or no expression of mRNAs for Th1 cytokines, TNF-.alpha., IL- 12p40, IGIF, and iNOS in the infected mice, but expression increased markedly after treatment with IL-12. In contrast, the mRNAs for Th2 cytokines, IL- 1.beta., and TGF-.beta. were detected at considerable levels during the early stages of infection, and, interestingly, expression was not suppressed by IL-12 but rather augmented, particularly during the late stage. Similar results were also obtained for IFN-.gamma., IL-4, IL-10, and TNF-.alpha. measured in the lung homogenates by enzyme-linked immunosorbent assay. These results suggest that the predominance of expression of Th2 cytokines and TGF-.beta. over Th1 cytokines, TNF-.alpha., IL-12p40, IGIF, and iNOS is associated with severe lethal infection in mice and that administration of IL-12 protects infected animals by stimulating Th1 cytokines.

CT Medical Descriptors:
*cryptococcosis
*host resistance
*infection resistance
*lung mycosis
animal experiment
animal model
article
cryptococcus neoformans
enzyme induction
female
gene expression regulation
helper cell
immunoregulation
immunostimulation
interferon production
mouse
nonhuman
priority journal
Drug Descriptors:
*gamma interferon: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
*interleukin 1beta: EC, endogenous compound
*interleukin 4: EC, endogenous compound
*interleukin 6: EC, endogenous compound
***nitric oxide synthase: EC, endogenous compound**
interleukin 10: EC, endogenous compound
messenger rna: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound

L21 ANSWER 9 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97000667 EMBASE
DN 1997000667
TI Immune responses to parasites: The art of distinguishing the good from the bad.

AU Moll H.
CS H. Moll, Res. Center for Infectious Diseases, University of Wurzburg, Rontgenring 11, D-97070 Wurzburg, Germany
SO Immunology Today, (1996) 17/12 (551-552).
ISSN: 0167-5699 CODEN: IMTOD8
CY United Kingdom
DT Journal; (Short Survey)
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
CT Medical Descriptors:
*immune response
*leishmania major
*parasitosis: ET, etiology
*parasitosis: DT, drug therapy
*schistosoma mansoni
*t lymphocyte
***vaccination**
gene control
mouse
nonhuman
priority journal
short survey
Drug Descriptors:
*gamma interferon: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
*interleukin 4: EC, endogenous compound
***nitric oxide: EC, endogenous compound**
*parasite antigen: EC, endogenous compound
*tumor necrosis factor alpha: EC, endogenous compound

L21 ANSWER 10 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96233303 EMBASE
DN 1996233303
TI Interleukin-12 gene-expression of macrophages is regulated by nitric oxide.
AU Rothe H.; Hartmann B.; Geerlings P.; Kolb H.
CS Diabetes Research Institute, Heinrich- Heine Univ. of Dusseldorf, Auf'm Hennekamp 65,D-40225 Dusseldorf, Germany
SO Biochemical and Biophysical Research Communications, (1996) 224/1 (159-163).
ISSN: 0006-291X CODEN: BBRCA
CY United States
DT Journal; Article
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB Interleukin-12 is a heterodimeric cytokine, mainly produced by macrophages. In our present study we demonstrate that interleukin-12 expression is regulated by nitric oxide. Incubation of the macrophage cell
line IC 21 with interferon-.gamma. gave rise to both interleukin-12 p40 mRNA and nitric oxide production. The concurrent addition of the nitric oxide synthase inhibitor N(G)-monomethyl-L-arginine inhibited nitrite production and in parallel completely suppressed interleukin-12 p40 mRNA

formation. This indicated that endogenous nitric oxide synthase activity was required for IL-12 p40 gene expression. Exposure of the cells towards the nitric oxide generating compounds nitroprusside or S-nitroso-N-acetyl-penicillamine induced interleukin-12 p40 mRNA. Maximal mRNA levels were induced with nitric oxide donors at 1 .mu.M concentration. We conclude that nitric oxide may exert an autoregulatory and paracrine control of interleukin-12 gene expression.

CT Medical Descriptors:
*gene expression regulation
animal cell
article
controlled study
gene induction
macrophage
mouse
nonhuman
priority journal
Drug Descriptors:
***interleukin 12**
*nitric oxide: EC, endogenous compound
gamma interferon
messenger rna: EC, endogenous compound
n acetyl s nitrosopenicillamine
n(g) methylarginine
nitric oxide synthase inhibitor
nitroprusside sodium

L21 ANSWER 11 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96157564 EMBASE
DN 1996157564
TI Indirect stimulatory effects of murine interleukin-12 on in vitro production of nitric oxide by mouse peritoneal cells.
AU Zidek Z.; Lotzova E.; Frankova D.; Savary C.A.
CS Department of Surgical Oncology, Texas Univ. M.D. Anderson Can. Ctr., Box 18, 1515 Holcombe Boulevard,Houston, TX 77030, United States
SO Journal of Interferon and Cytokine Research, (1996) 16/5 (389-393). ISSN: 1079-9907 CODEN: JICRFJ
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB The effect of murine interleukin- 12 (IL-12) on L-arginine-dependent biosynthesis of nitric oxide (NO) by mouse peritoneal cells was evaluated.
Interleukin-12 was found to trigger considerably enhanced production of NO
in a dose-dependent manner. Antibody neutralization studies indicated that
the effect of IL-12 was mediated by IFN-.gamma. without apparent participation of TNF- .alpha.. Synergistic effects of IL-12 plus lipopolysaccharide (LPS) were also observed. Our data thus provide evidence that IL-12 is a powerful but indirect modulator of NO formation. These findings may contribute to the better understanding of various biologic effects of IL-12.
CT Medical Descriptors:

***immunostimulation**
animal cell
animal experiment
animal tissue
antibody production
article
controlled study
dose response
drug mechanism
drug potentiation
female
immunopharmacology
mouse
nonhuman
peritoneum cell
priority journal
Drug Descriptors:
*interferon antibody: PD, pharmacology
***interleukin 12: IT, drug interaction**
***interleukin 12: PD, pharmacology**
*n(g) methylarginine: PD, pharmacology
***nitric oxide: EC, endogenous compound**
*tumor necrosis factor antibody: PD, pharmacology
arginine: PD, pharmacology
gamma interferon: EC, endogenous compound
lipopolysaccharide: IT, drug interaction
lipopolysaccharide: PD, pharmacology
tumor necrosis factor alpha: EC, endogenous compound

L21 ANSWER 12 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96031280 EMBASE
DN 1996031280
TI Production of nitric oxide (NO) is not essential for protection against acute Toxoplasma gondii infection in IRF-1(-/-) mice.
AU Khan I.A.; Matsuura T.; Fonseka S.; Kasper L.H.
CS Department of Medicine, Dartmouth Medical School,Hanover, NH 03755, United States
SO Journal of Immunology, (1996) 156/2 (636-643).
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Production of nitric oxide (NO) by macrophages is important for the killing of intracellular pathogens. IFN-.gamma. and LPS stimulate NO production by transcriptional up-regulation of inducible nitric oxide synthetase (iNOS). In the present study we used mice with a targeted disruption of the IFN regulatory factor-1 gene (IRF-1(-/-)) to investigate the importance of NO in the host immune response against Toxoplasma gondii, a major cause of infection in newborns and those with AIDS. IRF-1(-/-) mice were more susceptible to acute Toxoplasma infection, and

treatment with either exogenous IFN-.gamma. or in vivo neutralization of endogenous IFN-.gamma. had little effect on their susceptibility to infection. However, administration of exogenous IL-12 was able to prolong survival even when IFN-.gamma. was depleted. An in vivo depletion study suggested that the mechanism of this protective response is mediated in part by CD4+ T cells. The administration of IL-12 could not overcome the inhibition of lymphoproliferative response in T. gondii-infected mice and treatment with N-monomethyl-L-arginine (L-NMMA), a nitric oxide synthase (iNOS) antagonist in vitro was unable to reverse the immunosuppression. In response to Toxoplasma infection, splenocytes from IRF- 1(-/-) mice exhibited increased production of IL-10 as well as a 30-fold increase in its message expression. These studies indicate that NO may not be essential for host immunity to the parasite, and moreover that IL-12 appears to induce an IFN-.gamma.-independent mechanism of protection against this opportunistic pathogen.

CT Medical Descriptors:
*regulator gene
*toxoplasma gondii
*toxoplasmosis: PC, prevention
animal cell
animal experiment
animal model
article
controlled study
depletion
female
gene disruption
infection sensitivity
lymphocyte proliferation
mouse
nonhuman
priority journal
survival
Drug Descriptors:
*cd4 antigen: EC, endogenous compound
*gamma interferon
***interleukin 12**
*n(g) methylarginine
*nitric oxide: EC, endogenous compound
***nitric oxide synthase inhibitor**
cd8 antigen: EC, endogenous compound
concanavalin a
immunoglobulin g
interferon antibody
interleukin 10: EC, endogenous compound
messenger rna: EC, endogenous compound
nitrite: EC, endogenous compound

L21 ANSWER 13 OF 13 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95267825 EMBASE
DN 1995267825
TI IL-12-induced protection against blood-stage Plasmodium chabaudi AS requires IFN-.gamma. and TNF-.alpha. and occurs via a nitric oxide-dependent mechanism.
AU Stevenson M.M.; Mi Fong Tam; Wolf S.F.; Sher A.
CS Montreal Gen. Hosp. Research Inst., 1650 Cedar Avenue,Montreal, Que. H3G

1A4, Canada
SO Journal of Immunology, (1995) 155/5 (2545-2556).
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB The effects of IL-12 administration on the development of protective immunity to blood-stage Plasmodium chabaudi AS were analyzed. Treatment of susceptible A/J mice on the day of infection and for 5 days postinfection with various doses (0.025-0.3 .mu.g) of rIL-12 significantly decreased the peak parasitemia level, but only treatment with 0.1 .mu.g resulted in increased survival. Treatment of resistant 86 mice with 0.1 .mu.g of rIL-12 using the same regimen also significantly decreased the peak parasitemia level, but 40% of the animals died. Treatment of these mice with anti-IL-12 mAb resulted in a more severe course of infection, but survival was not significantly altered. The mechanism of IL-12-induced resistance was examined in A/J mice during infection. Compared with spleen cells from untreated mice, cells from IL-12-treated mice produced significantly higher levels of IFN-.gamma. spontaneously as well as in response to Con A or Ag stimulation on day 7 postinfection. Significantly higher levels of IFN-.gamma. and TNF-.alpha. were found in the sera of IL-12-treated mice, which correlated with high levels of the nitric oxide (NO) metabolite, NO3-. Furthermore, CD4+ T cell depletion was found to abrogate IL-12-induced resistance. Administration of neutralizing mAb against IFN-.gamma. or TNF-.alpha. to IL-12-treated mice showed that simultaneous depletion of both cytokines resulted in 100% mortality. The role of NO was investigated by administration of aminoguanidine, a selective inhibitor of cytokine-inducible nitric oxide synthase, to IL-12-treated mice. Significantly increased mortality was observed following treatment twice daily with 9 mg of aminoguanidine, but there was no effect on parasitemia. In conclusion, these results demonstrate that IL-12 regulates the development of resistance to P. chabaudi AS via a CD4+ Th1 response, which involves the cytokines IFN-.gamma. and TNF-.alpha., and is in part NO dependent. Therefore, IL-12, given in the appropriate dose, may be useful in the induction of protective immunity to blood-stage malaria.
CT Medical Descriptors:
*malaria: ET, etiology
animal experiment
antimalarial activity
article
controlled study
female
immunostimulation
infection resistance
male
mouse
nonhuman
plasmodium chabaudi

priority journal
Drug Descriptors:
*gamma interferon: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
***nitric oxide: EC, endogenous compound**
*tumor necrosis factor alpha: EC, endogenous compound

L22 ANSWER 1 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000342967 EMBASE
TI The combined action of IL-15 and IL-12 gene transfer can induce tumor cell
rejection without T and NK cell involvement.
AU Di Carlo E.; Comes A.; Basso S.; De Ambrosis A.; Meazza R.; Musiani P.; Moelling K.; Albini A.; Ferrini S.
CS Dr. S. Ferrini, Centro di Biotecnologie Avanzate, Largo Rosanna Benzi no. 10, 16132 Genova, Italy. ferrini@ermes.cba.unige.it
SO Journal of Immunology, (15 Sep 2000) 165/6 (3111-3118).
Refs: 56
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB The cooperative antitumor effects of IL-12 and IL-15 gene transfer were studied in the N592 MHC class I-negative small cell lung cancer cell line xenotransplanted in nude mice. N592 cells engineered to secrete IL-15 displayed a significantly reduced tumor growth kinetics, and a slightly reduced tumor take rate, while N592 engineered with IL-12 displayed only minor changes in their growth in nude mice. However, N592 cells producing both cytokines were completely rejected, and produced a potent local bystander effect, inducing rejection of coinjected wild-type tumor cells. N592/IL-12/IL-15 cells were completely and promptly rejected also in NK-depleted nude mice, while in granulocyte-depleted animals a slight delay in the rejection process was observed. Immunohistochemical analyses of the N592/IL-12/IL-15 tumor area in intact nude mice revealed the presence of infiltrating macrophages, granulocytes, and NK cells, and expression of inducible NO synthase and of secondary cytokines such as IL-1.beta., TNF-.alpha., and IFN-.gamma., and at higher levels GM-CSF, macrophage-inflammatory protein-2, and monocyte chemoattractant protein-1.
In NK cell-depleted nude mice, numerous macrophages and granulocytes infiltrated the tumor, and a strong expression of macrophage-inflammatory protein-2 and inducible NO synthase was also observed. Finally, macrophages cocultured with N592/IL-12/1L-15 produced NO in vitro, and **inhibited** tumor cell growth, further suggesting their role as effector cells in this model.
CT Medical Descriptors:
*gene transfer
*natural killer cell
*major histocompatibility complex
*tumor immunity
*T lymphocyte
nude mouse

lung small cell cancer
tumor growth
xenograft
antineoplastic activity
protein expression
effector cell
immunohistochemistry
gene therapy
nonhuman
animal experiment
animal model
animal cell
article
priority journal
Drug Descriptors:
*interleukin 15
***interleukin 12**
nitric oxide synthase: EC, endogenous compound
macrophage inflammatory protein 2: EC, endogenous compound
interleukin 1beta

L22 ANSWER 2 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000166948 EMBASE
TI Blockade of costimulation prevents infection-induced immunopathology in interleukin-10-deficient mice.
AU Villegas E.N.; Wlle U.; Craig L.; Linsley P.S.; Rennick D.M.; Peach R.; Hunter C.A.
CS C.A. Hunter, Department of Pathobiology, University of Pennsylvania, School of Veterinary Medicine, 3800 Spruce St., Philadelphia, PA 19104-6008, United States. chunter@phl.vet.upenn.edu
SO Infection and Immunity, (2000) 68/5 (2837-2844).
Refs: 56
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LA English
SL English
AB Interleukin-10 (IL-10) is associated with **inhibition** of cell-mediated immunity and downregulation of the expression of costimulatory molecules required for T-cell activation. When IL-10-deficient (IL-10KO) mice are infected with Toxoplasma gondii, they succumb to a T-cell-mediated shock-like reaction characterized by the overproduction of IL-12 and gamma interferon (IFN-.gamma.) associated with widespread necrosis of the liver. Since costimulation is critical for T-cell activation, we investigated the role of the CD28-B7 and CD40-CD40 ligand (CD40L) interactions in this infection- induced immunopathology. Our studies show that infection of mice with T. gondii resulted in increased expression of B7 and CD40 that was similar in wild-type and IL-10KO mice. In vivo blockade of the CD28-B7 or CD40-CD40L interactions following infection of IL-10KO mice with T. gondii did not affect serum levels of IFN-.gamma. or IL-12, nor did it prevent death in these mice. However, when both pathways were blocked, the IL-10KO mice survived the acute phase of infection and had reduced serum levels of IFN-y and alanine

transaminase as well as decreased expression of inducible nitric oxide synthase in the liver and spleen. Analysis of parasite-specific recall responses from infected IL-10KO mice revealed that blockade of the CD40-CD40L interaction had minimal effects on cytokine production, whereas blockade of the CD28-B7 interaction resulted in decreased production of IFN-.gamma. but not IL-12. Further reduction of FiN-.gamma. production was observed when both costimulatory pathways were blocked. Together, these results demonstrate that the CD28-B7 and CD40-CD40L interactions are involved in the development of infection-induced immunopathology in the absence of IL-10.

CT Medical Descriptors:
*immunopathology
*toxoplasmosis
*T lymphocyte activation
cellular immunity
down regulation
Toxoplasma gondii
cytokine production
antigen expression
cytotoxic T lymphocyte
nonhuman
female
mouse
animal experiment
animal model
controlled study
animal tissue
article
priority journal
Drug Descriptors:
*interleukin 10
***interleukin 12: EC, endogenous compound**
*gamma interferon: EC, endogenous compound
*CD28 antigen: EC, endogenous compound
*CD40 antigen: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
alanine aminotransferase: EC, endogenous compound

L22 ANSWER 3 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999435728 EMBASE
TI Extracellular signal-related kinase (ERK) and p38 mitogen-activated protein (MAP) kinases differentially regulate the lipopolysaccharide-mediated induction of inducible nitric oxide synthase and IL-12 in macrophages: Leishmania phosphoglycans subvert macrophage IL-12 production by targeting ERK MAP kinase.
AU Feng G.-J.; Goodridge H.S.; Harnett M.M.; Wei X.-Q.; Nikolaev A.V.; Higson A.P.; Liew F.-Y.
CS Dr. F.-Y. Liew, Department of Immunology, University of Glasgow, Glasgow G11 6NT, United Kingdom. f.y.liew@clinmed.gla.ac.uk
SO Journal of Immunology, (1999) 163/12 (6403-6412).
Refs: 55
ISSN: 0022-1767 CODEN: JOIMA3
CY United States

DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Macrophage activation by cytokines or microbial products such as LPS results in the induction and release of several key immune effector molecules including NO and IL-12. These have been shown to play crucial roles in the development of immunity to intracellular pathogens such as Leishmania. The molecular mechanisms underlying the induction of these effector molecules are not fully understood. We now show that the extracellular signal-related kinase (ERK) and p38 mitogen-activated protein (MAP) kinases play differential roles in the regulation of LPS-stimulated inducible NO synthase and IL-12 gene expression. In macrophages, LPS stimulates the simultaneous activation of all three classes of MAP kinases, ERK, c-jun N-terminal kinase, and p38, albeit with differential activation kinetics. However, studies using **inhibitors** selective for ERK (PD98059) and p38 (SB203580) show that while p38 plays an essential role in the induction of inducible NO synthase, ERK MAP kinases play only a minor role in promoting NO generation. In contrast, while p38 promotes induction of IL-12 (p40) mRNA, ERK activation suppresses LPS- mediated IL-12 transcription. The biological relevance of these regulatory signals is demonstrated by our finding that Leishmania lipophosphoglycans, which promote parasite survival, act by stimulating ERK MAP kinase to **inhibit** macrophage IL-12 production. Thus, as ERK and p38 MAP kinases differentially regulate the induction of the macrophage effector molecules, inducible NO synthase and IL-12, these kinases are potential targets not only for the development of novel strategies to combat intracellular pathogens but also for therapeutic immunomodulation.
CT Medical Descriptors:
*cytokine production
*leishmaniasis
*immunomodulation
peritoneum macrophage
enzyme induction
protein targeting
macrophage activation
inflammation
parasite survival
nonhuman
mouse
controlled study
animal cell
article
priority journal
Drug Descriptors:
*mitogen activated protein kinase
*synaptophysin
***interleukin 12**
*lipophosphoglycan
***nitric oxide synthase**
lipopolysaccharide

L22 ANSWER 4 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 1999431448 EMBASE
TI Antifungal type 1 responses are upregulated in IL-10-deficient mice.
AU Del Sero G.; Mencacci A.; Cenci E.; D'Ostiani C.F.; Montagnoli C.; Bacci A.; Mosci P.; Kopf M.; Romani L.
CS L. Romani, Microbiology Section, Dept. of Exp. Med. and Biochem. Sci., University of Perugia, I-06122 Perugia, Italy
SO Microbes and Infection, (1999) 1/14 (1169-1180).
Refs: 82
ISSN: 1286-4579 CODEN: MCINFS
CY France
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB C57BL/6 mice are highly resistant to infections caused by Candida albicans and Aspergillus fumigatus. To elucidate the role of IL-10 produced by C57BL/6 mice during these infections, parameters of infection and immunity to it were evaluated in IL-10-deficient and wild-type mice with disseminated or gastrointestinal candidiasis or invasive pulmonary aspergillosis. Unlike parasitic protozoan infection, C. albicans or A. fumigatus infection did not induce significant acute toxicity in IL-10-deficient mice, who, instead, showed reduced fungal burden and fungal-associated inflammatory responses. The increased resistance to infections as compared to wild-type mice was associated with upregulation of innate and acquired antifungal Th1 responses, such as a dramatically higher production of IL-12, nitric oxide (NO) and TNF- .alpha. as well as IFN-.gamma. by CD4+ T cells. Pharmacological **inhibition** of NO production greatly reduced resistance to gastrointestinal candidiasis, thus pointing to the importance of IL-10-dependent NO regulation at mucosal sites in fungal infections. These results are reminiscent of those obtained in genetically susceptible mice, in which IL-10 administration increased, and IL-10 neutralization decreased, susceptibility to C. albicans and A. fumigatus infections. Collectively, these observations indicate that the absence of IL-10 augments innate and acquired antifungal immunity by upregulating type 1 cytokine responses. The resulting protective Th1 responses lead to a prompt reduction of fungal growth, thus preventing tissue destruction and lethal levels of proinflammatory cytokines.
CT Medical Descriptors:
*immune response
*cytokine production
*candidiasis: ET, etiology
*lung aspergillosis: ET, etiology
helper cell
knockout mouse
infection resistance
candida albicans
aspergillus fumigatus
inflammation
genetic susceptibility
cellular immunity

nonhuman
male
female
mouse
animal experiment
animal model
animal tissue
animal cell
article
priority journal
Drug Descriptors:
***interleukin 12: EC, endogenous compound**
nitric oxide: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
gamma interferon: EC, endogenous compound

L22 ANSWER 5 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999267907 EMBASE
TI IL-12 as a therapeutic target for pharmacological modulation in immune-mediated and inflammatory diseases: Regulation of T helper 1/T helper 2 responses.
AU Hasko G.; Szabo C.
CS G. Hasko, Inotek Corp, 100 Cummings Center, Beverly, Massachusetts, MA 01915, United States. ghasko@inotekcorp.com
SO British Journal of Pharmacology, (1999) 127/6 (1295-1304).
Refs: 129
ISSN: 0007-1188 CODEN: BJPCBM
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB 1. Interleukin-12 (IL-12) is a pivotal cytokine in driving the immune system towards a T helper (Th)1 type response and preventing a Th2 type immune profile. Therefore, IL-12 is indispensable in the defense against certain, mainly intracellular pathogens, but overproduction of this cytokine is crucially involved in the etiology of several inflammatory and autoimmune diseases. 2. Hence, IL-12 is an ideal target for pharmacological intervention in the therapy of autoimmune and inflammatory diseases. 3. The production of IL-12 and a resultant Th1 type immune response can be suppressed with several pharmacological approaches including modulation of intracellular cyclic AMP levels, glucocorticoids and nuclear factor-.kappa.B **inhibition**. IL-12 responsiveness may be **inhibited** using anti-IL-12 antibodies, soluble IL-12 receptors or the IL-12 p46 homodimer. 4. Exploitation of these approaches may provide novel means for the experimental therapy of a variety of pathophysiological states.
CT Medical Descriptors:
*immunomodulation
*immunopathology
*inflammation
*helper cell
cellular immunity

host resistance
autoimmune disease: ET, etiology
drug targeting
signal transduction
human
nonhuman
review
priority journal
Drug Descriptors:
***interleukin 12: EC, endogenous compound**
cyclic AMP: EC, endogenous compound
glucocorticoid: DV, drug development
glucocorticoid: PD, pharmacology
immunoglobulin enhancer binding protein: EC, endogenous compound
interleukin 12 receptor: DV, drug development
protein p40: DV, drug development
protein p40: PD, pharmacology
cytokine antibody: DV, drug development
cytokine antibody: PD, pharmacology
nitric oxide: EC, endogenous compound
immunosuppressive agent: DV, drug development
immunosuppressive agent: PD, pharmacology
salbutamol: PD, pharmacology
prostaglandin e2: PD, pharmacology
calcitonin gene related peptide: PD, pharmacology
dexamethasone: PD, pharmacology
hydrocortisone: PD, pharmacology
clobetasol: PD, pharmacology
acetylsalicylic acid: PD, pharmacology
n(g) methylarginine: PD, pharmacology
captopril: PD, pharmacology
lisinopril: PD, pharmacology
adenosine: PD, pharmacology
glibenclamide: PD, pharmacology

L22 ANSWER 6 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999232937 EMBASE
TI Macrophage control of herpes simplex virus type 1 replication in the peripheral nervous system.
AU Kodukula P.; Liu T.; Van Rooijen N.; Jager M.J.; Hendricks R.L.
CS Dr. R.L. Hendricks, Univ. of Pittsburgh Sch. of Medicine, 915 Eye and Ear Institute, 203 Lothrop Street, Pittsburgh, PA 15213-2588, United States. hendricksRR@MSX.UPMC.edu
SO Journal of Immunology, (1 Mar 1999) 162/5 (2895-2905).
Refs: 24
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English
AB After corneal infection, herpes simplex virus type 1 (HSV-1) invades sensory neurons with cell bodies in the trigeminal ganglion (TG), replicates briefly, and then establishes a latent infection in these neurons. HSV-1 replication in the TG can be detected as early as 2 days

after corneal infection, reaches peak titers by 3-5 days after infection, and is undetectable by 7-10 days. During the period of HSV-1 replication, macrophages and .gamma..delta. TCR+ T lymphocytes infiltrate the TG, and TNF-.alpha., IFN- .gamma., the inducible nitric oxide synthase (iNOS) enzyme, and IL-12 are expressed. TNF-.alpha., IFN-.gamma., and the iNOS product nitric oxide (NO) all **inhibit** HSV-1 replication in vitro. Macrophage and .gamma..delta. TCR+ T cell depletion studies demonstrated that macrophages are the main source of TNF-.alpha. and iNOS, whereas .gamma..delta. TCR+ T cells produce IFN-.gamma.. Macrophage depletion, aminoguanidine **inhibition** of iNOS, and neutralization of TNF-.alpha. or IFN-.gamma. all individually and synergistically increased HSV-1 titers in the TG after HSV- 1 corneal infection. Moreover, individually depleting macrophages or neutralizing TNF-.alpha. or IFN-.gamma. markedly reduced the accumulation of both macrophages and .gamma..delta. TCR+ T cells in the TG. Our findings establish that after primary HSV-1 infection, the bulk of virus replication in the sensory ganglia is controlled by macrophages and .gamma..delta. TCR+ T lymphocytes through their production of antiviral molecules TNF-.alpha., NO, and IFN-.gamma.. Our findings also strongly suggest that cross-regulation between these two cell types is necessary for their accumulation and function in the infected TG.

CT Medical Descriptors:
*herpes simplex virus 1
*peripheral nervous system
*virus replication
macrophage
trigeminus ganglion
eye infection
t lymphocyte
interferon production
nonhuman
female
mouse
animal experiment
animal cell
article
priority journal
Drug Descriptors:
*t lymphocyte receptor: EC, endogenous compound
*tumor necrosis factor alpha: EC, endogenous compound
*gamma interferon: EC, endogenous compound
***nitric oxide synthase: EC, endogenous compound**
***interleukin 12: EC, endogenous compound**

L22 ANSWER 7 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999231196 EMBASE
TI Different doses of adenoviral vector expressing IL-12 enhance or depress the immune response to a coadministered antigen: The role of nitric oxide.
AU Lasarte J.J.; Corrales F.J.; Casares N.; De Cerio A.L.-D.; Qian C.; Xie X.; Borras-Cuesta F.; Prieto J.
CS Dr. J. Prieto, Department of Medicine, Liver Unit, University of Navarra, 31008 Pamplona, Spain. jprieto@unav.es
SO Journal of Immunology, (1 May 1999) 162/9 (5270-5277).

Refs: 50
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English

AB Joint immunization with two recombinant adenoviruses, one expressing hepatitis C virus (HCV) core and E1 proteins and another expressing IL-12 (RAdIL-12), strongly potentiates cellular immune response against HCV Ags in BALB/c mice when RAdIL-12 was used at doses of 1 x 105-1 x 107 plaque-forming units. However, cellular immunity against HCV Ags was abolished when higher doses (1 x 108 plaque-forming units) of RAdIL-12 were used. This immunosuppressive effect was associated with marked elevation of IFN-.gamma. and nitric oxide in the serum and increased cell apoptosis in the spleen. Administration of N-nitro-L-arginine methyl ester (L-NAME), an **inhibitor** of nitric oxide synthase, to mice that received high doses of RAdIL-12 was lethal, whereas no apparent systemic toxicity by L-NAME was observed in those immunized with lower doses of the adenovirus.

Interestingly, in mice immunized with recombinant adenovirus expressing core and E1 proteins of HCV in combination with RAdIL-12 at low doses (1 x 107 plaque-forming units), L- NAME **inhibited** T cell proliferation and CTL activity in response to HCV Ags and also production of Abs against adenoviral proteins. In conclusion, gene transfer of IL-12 can increase or abolish cell immunity against an Ag depending of the dose of the vector expressing the cytokine. IL-12 stimulates the synthesis of NO which is needed for the immunostimulating effects of IL- 12, but apoptosis of T cells and immunosuppression ensues when IFN-.gamma. and NO are generated at very high concentrations.

CT Medical Descriptors:
*virus immunity
*protein expression
virus vector
immune response
hepatitis c virus
dose response
plaque forming cell
enzyme inhibition
gene transfer
cytokine production
nonhuman
mouse
animal experiment
controlled study
animal tissue
animal cell
intraperitoneal drug administration
article
priority journal
Drug Descriptors:
***interleukin 12: EC, endogenous compound**
*virus antigen: EC, endogenous compound
virus protein: EC, endogenous compound

gamma interferon: EC, endogenous compound
nitric oxide: EC, endogenous compound
interleukin 2: EC, endogenous compound
glutathione: EC, endogenous compound
n(g) nitroarginine methyl ester: DO, drug dose
n(g) nitroarginine methyl ester: PD, pharmacology

L22 ANSWER 8 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999192775 EMBASE
TI Immunopathology of inflammatory neuropathies.
AU Oka N.
CS Dr. N. Oka, Department of Neurology, Kyoto University Hospital, Kyoto, Japan
SO Clinical Neurology, (1999) 39/1 (90-91).
Refs: 7
ISSN: 0009-918X CODEN: RISHDJ
CY Japan
DT Journal; Conference Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
037 Drug Literature Index
LA Japanese
SL English; Japanese
AB With the use of immunohistochemical technique, nerve biopsy is more informative for the diagnosis of inflammatory neuropathies. In chronic inflammatory demyelinating neuropathy, an increased number of T cells are frequently present in endoneurium, which is in contrast to hereditary neuropathies. In active demyelinating lesions, macrophages adhering nerve fibers showed stainings with TNF-.alpha., NOS and cyclooxygenase-2 (COX-2). These molecules may act in concert to promote nerve damage. The **inhibitor** of COX- 2, nimesulide, was effective on experimental allergic neuritis, even if given after the onset of clinical signs. A COX-2 **inhibitor** may have potential as an additional therapeutic agent in human inflammatory neuropathies. In vasculitic neuropathies, cell-mediated cytotoxicity may be involved in the pathogenesis of small vessel injury. Axonal injury may be caused by focal ischemia. However, an immune attack might be involved in nerve damage, since T cells and IL-12 positive cells were found in endoneurium of some patients with active vasculitis.
CT Medical Descriptors:
*neuropathy: DI, diagnosis
*neuropathy: ET, etiology
*chronic inflammation: DI, diagnosis
*immunopathology
immunohistochemistry
nerve biopsy
demyelinating neuropathy: ET, etiology
t lymphocyte
endoneurium
familial disease
macrophage
allergic neuropathy: ET, etiology
vasculitis
cell mediated cytotoxicity
ischemia
human
nonhuman

conference paper
Drug Descriptors:
*nimesulide
***cyclooxygenase 2 inhibitor**
*tumor necrosis factor alpha: EC, endogenous compound
***nitric oxide synthase: EC, endogenous compound**
*cyclooxygenase 2: EC, endogenous compound
***interleukin 12: EC, endogenous compound**

L22 ANSWER 9 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999150689 EMBASE
TI Role of TNF-.alpha. in the induction of fungicidal activity of mouse peritoneal exudate cells against Cryptococcus neoformans by IL-12 and IL-18.
AU Kawakami K.; Qureshi M.H.; Koguchi Y.; Zhang T.; Okamura H.; Kurimoto M.; Saito A.
CS K. Kawakami, First Dept. of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa 903-0215, Japan
SO Cellular Immunology, (10 Apr 1999) 193/1 (9-16).
Refs: 43
ISSN: 0008-8749 CODEN: CLIMB8
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB We nave recently demonstrated that two IFN-.gamma.-inducing cytokines, interleukin (IL)-12 and IL-18, synergistically induced the fungicidal activity of mouse peritoneal exudate cells (PEC) against Cryptococcus neoformans through NK cell production of interferon (IFN)-.gamma. and nitric oxide (NO) synthesis. In the present study, we further dissected these effects by examining the involvement of tumor necrosis factor (TNF)-.alpha. in the induction of IL-12/IL-18-stimulated PEC fungicidal activity. The addition of neutralizing anti-TNF-.alpha. mAb significantly suppressed IL-12/IL-18-stimulated PEC anticryptococcal activity. This effect was ascribed to the **inhibition** of macrophage NO synthesis, but not of IFN-.gamma. production by NK cells, because the same treatment **inhibited** the former response, but not the latter one. On the other hand, combined treatment with IL-12 and IL-18 synergistically induced the production of TNF-.alpha. by PEC and this effect was almost completely abrogated by neutralizing anti-IFN-.gamma. mAb. The cell type producing TNF-.alpha. among PEC was mostly macrophage. TNF-.alpha. significantly promoted macrophage NO production and anticryptococcal activity induced by IFN-.gamma., and furthermore anti-TNF-.alpha. mAb partially **inhibited** these responses. Considered together, our results indicated that TNF-.alpha. contributed to the potentiation of IL-12/IL- 18-induced PEC fungicidal activity against C. neoformans through enhancement of IFN-.gamma.-induced production of NO by macrophages, but not through increased production of IFN-.gamma. by NK cells.
CT Medical Descriptors:
*peritoneal exudate cell
*cryptococcus neoformans
fungicidal activity
cytokine production

macrophage
natural killer cell
nonhuman
mouse
controlled study
animal cell
article
priority journal
Drug Descriptors:
*tumor necrosis factor alpha: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
*interleukin 18: EC, endogenous compound
nitric oxide: EC, endogenous compound
gamma interferon: EC, endogenous compound

L22 ANSWER 10 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1999101467 EMBASE
TI Adenovirus-mediated interleukin-12 gene therapy for prostate cancer: Suppression of orthotopic tumor growth and pre-established lung metastases in an orthotopic model.
AU Nasu Y.; Bangma C.H.; Hull G.W.; Lee H.-M.; Hu J.; Wang J.; McCurdy M.A.; Shimura S.; Yang G.; Timme T.L.; Thompson T.C.
CS T.C. Thompson, Scott Department of Urology, Baylor College of Medicine, 6560 Fannin, Houston, TX 77030, United States
SO Gene Therapy, (1999) 6/3 (338-349).
Refs: 42
ISSN: 0969-7128 CODEN: GETHEC
CY United Kingdom
DT Journal; Article
FS 016 Cancer
022 Human Genetics
028 Urology and Nephrology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Interleukin-12 (IL-12) can elicit potent antitumoral effects that involve the recruitment of specific immune effector cells. We investigated the efficacy o a single injection of a recombinant adenovirus expressing murine IL-12 (AdmIL-12) directly into orthoptic mouse prostrate carcinomas generated from a poorly immunogenic cell line (RM-9) derived from the mouse prostrate reconstitution system. Significant growth suppression (> 50% reduction of tumor weight) and increased mean survival time (23.4 to 28.9 days) were observed compared with controls. Suppression of pre-established lung metastases was also observed following the injection of AdmIL-12 into the orthoptic tumor. Cytolytic natural killer cell activity was markedly enhanced 1-2 days after virus injection. Immunohistochemical analysis showed significantly elevated intratumoral infiltration of CD4+ and CD8+ T cells 7 days after virus injection. However, splenocyte-derived cytotoxic T lymphocytes were not defected during the 14 days following treatment. Increased numbers of nitric oxide synthase-positive macrophages were seen in the AdmIL-12 treated group 7 days following injection. Systemic **inhibition** of natural killer cells with anti-asialo-GM1 serum led to increased numbers of lung metastases in AdmIL-12-treated orthotopic tumors but did not affect local

tumor growth. In this model system the anti-tumor effects of a single injection of adenovirus-mediated IL-12 appears to be based to a large extent on the activation of nitric oxide synthase in macrophages and possibly T cell activities, whereas the relatively early cytolytic activity of natural killer cells are largely but not exclusively responsible for the antimetastatic effects.

CT Medical Descriptors:
*gene therapy
*prostate cancer: DT, drug therapy
adenovirus
tumor growth
lung metastasis: CO, complication
antineoplastic activity
immunocompetent cell
growth inhibition
cancer inhibition
survival time
cancer survival
immunohistochemistry
cytotoxic t lymphocyte
macrophage
natural killer cell
cytolysis
enzyme activity
cell infiltration
antigen expression
dose response
nonhuman
male
mouse
animal experiment
animal model
controlled study
animal cell
intratumoral drug administration
article
priority journal
Drug Descriptors:
***interleukin 12: DT, drug therapy**
cd4 antigen: EC, endogenous compound
cd8 antigen: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
major histocompatibility antigen class 1: EC, endogenous compound

L22 ANSWER 11 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998417470 EMBASE
TI Nitric oxide regulates Th1 cell development through the **inhibition** of IL-12 synthesis by macrophages.
AU Huang F.-P.; Niedbala W.; Wei X.-Q.; Xu D.; Feng G.-J.; Robinson J.H.; Lam C.; Liew F.Y.
CS F.Y. Liew, Department of Immunology, University of Glasgow, Glasgow G11 6NT, United Kingdom. f.y.liew@clinmed.gla.ac.uk
SO European Journal of Immunology, (1998) 28/12 (4062-4070).
Refs: 41
ISSN: 0014-2980 CODEN: EJIMAF
CY Germany

DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB We have previously reported that mice lacking inducible nitric oxide synthase (NOS2) developed enhanced Th1 cell responses. We now investigated the mechanism by which NO modulates Th1 cells differentiation. Peritoneal macrophages from NOS2-deficient mice infected with Leishmania major in vivo or stimulated with IFN-.gamma. or lipopolysaccharide (LPS) in vitro produced significantly higher levels of IL-12 than those from heterozygous or wild-type mice. A macrophage cell line, J774, produced significant amounts of IL-12 following activation with LPS, or LPS plus IFN-.gamma.. This could be markedly enhanced by the NOS **inhibitor** L-N(G) monomethyl arginine (L-NMMA), but profoundly **inhibited** by the NO-generating compound S-nitroso-N-acetyl-penicillamine (SNAP). The effect of NO in this system is selective, since SNAP enhanced and L-NMMA decreased TNF-.alpha. synthesis by LPS-activated J774 cells. The differential effect of NO on IL-12 and TNF-.alpha. is at the transcriptional level and is activation dependent. Since IL-12 is a major inducer of Th1 cells which produce IFN-.gamma. that can activate macrophages to produce IL-12, our data demonstrate that NO can be an **inhibitor** of this feedback loop, preventing the excessive amplification of Th1 cells which are implicated in a range of immunopathologies.
CT Medical Descriptors:
*helper cell
*peritoneum macrophage
cell differentiation
leishmania major
heterozygote
feedback system
nonhuman
mouse
animal experiment
animal model
controlled study
animal cell
article
priority journal
Drug Descriptors:
***nitric oxide: EC, endogenous compound**
***interleukin 12: EC, endogenous compound**
gamma interferon
lipopolysaccharide
n(g) methylarginine
n acetyl s nitrosopenicillamine
tumor necrosis factor alpha: EC, endogenous compound

L22 ANSWER 12 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998368426 EMBASE
TI An agonist of adenosine A3 receptors decreases interleukin-12 and interferon-.gamma. production and prevents lethality in endotoxemic mice.

AU Hasko G.; Nemeth Z.H.; Vizi E.S.; Salzman A.L.; Szabo C.
CS G. Hasko, Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, Budapest, Hungary
SO European Journal of Pharmacology, (9 Oct 1998) 358/3 (261-268).
Refs: 46
ISSN: 0014-2999 CODEN: EJPHAZ
PUI S 0014-2999(98)00619-0
CY Netherlands
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We have recently observed that the selective adenosine A3 receptor agonist N6-(3-iodobenzyl)-adenosine-5'-N-methyluronamide (IB-MECA) augments interleukin-10 and **inhibits** tumor necrosis factor-.alpha. production in endotoxemic mice. In the present study, we extended our investigations into the effect of this compound on the bacterial lipopolysaccharide (endotoxin)-induced inflammatory response in the BALB/c, as well as in the C57BL/6 interleukin-10(+/+) and the interleukin-10 deficient C57BL/6 interleukin-10(0/0) mice strains. In the BALB/c mice, i.p. pre-treatment with IB-MECA (0.2 and 0.5 mg/kg) decreased lipopolysaccharide (60 mg/kg i.p.)-induced plasma levels of interleukin-12 (p40 and p70), interferon-.gamma., and nitrite/nitrate (breakdown products of nitric oxide (NO)). On the other hand, pre-treatment with this compound failed to influence lipopolysaccharide-induced plasma interleukin-1.alpha., interleukin-6, and corticosterone concentrations. Similar to its effect in BALB/c mice, IB-MECA enhanced the release of interleukin-10 in the C57BL/6 interleukin-10(+/+) mice. Furthermore, IB-MECA **inhibited** the production of interleukin-12, interferon-.gamma., and NO in both the C57BL/6 interleukin-10(+/+) and C57BL/6 interleukin-10(0/0) mice, suggesting that the **inhibition** of pro-inflammatory cytokine production by this compound is independent of the increased release of interleukin-10. Finally, pre-treatment with this compound protected mice against lipopolysaccharide (60 mg/kg i.p.)-induced lethality. These results indicate that stimulation of adenosine A3 receptors has potent anti-inflammatory effects and may represent a potential strategy in the treatment of septic shock and other inflammatory diseases.
CT Medical Descriptors:
*endotoxemia: ET, etiology
*endotoxemia: TH, therapy
lethality
inflammation: ET, etiology
cytokine release
septic shock: TH, therapy
nonhuman
male
mouse

animal experiment
animal model
controlled study
intraperitoneal drug administration
article
priority journal
Drug Descriptors:
*adenosine a3 receptor: EC, endogenous compound
*adenosine receptor stimulating agent: PD, pharmacology
***interleukin 12: EC, endogenous compound**
*gamma interferon: EC, endogenous compound
interleukin 10: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
bacterium lipopolysaccharide: TO, drug toxicity
6 n (3 iodobenzyl)adenosine 5' n methylcarboxamide: PD, pharmacology
nitric oxide: EC, endogenous compound
nitrite: EC, endogenous compound
nitrate: EC, endogenous compound
interleukin 1alpha: EC, endogenous compound
interleukin 6: EC, endogenous compound
corticosterone: EC, endogenous compound

L22 ANSWER 13 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998285863 EMBASE
TI Vasoactive intestinal peptide **inhibits** IL-12 and nitric oxide production in murine macrophages.
AU Xin Z.; Sriram S.
CS S. Sriram, Multiple Sclerosis Research Lab., Vanderbilt Stallworth Rehab. Hosp., 2201 Capers Avenue, Nashville, TN 37212, United States. srirams@ctrvax.vanderbilt.edu
SO Journal of Neuroimmunology, (14 Aug 1998) 89/1-2 (206-212).
Refs: 43
ISSN: 0165-5728 CODEN: JNRIDW
PUI S 0165-5728(98)00140-4
CY Netherlands
DT Journal; Article
FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English
AB Vasoactive intestinal peptide (VIP) is a naturally occurring neuropeptide widely distributed in the nervous system. In this study, we investigated the effect of VIP on IL-12, TNF alpha and nitric oxide (NO) production in macrophages following activation with lipopolysaccharide (LPS) or superantigens. In vitro studies show that at physiologic concentrations, VIP **inhibited** IL-12 and NO but not TNF alpha production in macrophages which were stimulated with LPS or superantigens. The **inhibitory** effect of VIP on IL-12 production appeared to be cAMP mediated since other cAMP inducing agents were also potent in **inhibiting** IL-12 production. Since IL-12 plays a critical role in T cell function, we suggest that naturally occurring neural hormones can regulate the type and direction of the immune response.
CT Medical Descriptors:
*peritoneum macrophage
autoimmune disease: ET, etiology
macrophage activation
immunoregulation

immune response
nervous system
gastrointestinal tract
nonhuman
mouse
controlled study
animal cell
article
priority journal
Drug Descriptors:
***nitric oxide: EC, endogenous compound**
***interleukin 12: EC, endogenous compound**
*vasoactive intestinal polypeptide
cytokine: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
bacterium lipopolysaccharide
recombinant interleukin 12
gamma interferon

L22 ANSWER 14 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998284349 EMBASE
TI Low dose TGF-.beta. attenuates IL-12 responsiveness in murine Th cells.
AU Gorham J.D.; Guler M.L.; Fenoglio D.; Gubler U.; Murphy K.M.
CS Dr. K.M. Murphy, Department of Pathology, Washington Univ. School of Medicine, 660 South Euclid Ave., St. Louis, MO 63110, United States. murphy@immunology.wustl.edu
SO Journal of Immunology, (15 Aug 1998) 161/4 (1664-1670).
Refs: 61
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Expression of IL-12Rs is one important checkpoint for Th1 development. BALB/c DO11.10 CD4+ T cells stimulated by Ag in neutral conditions lose expression of the IL-12R .beta.2 subunit and become unresponsive to IL-12.
In contrast, B10.D2 or F1 (BALB/c x B10.D2) DO11.10 CD4+ T cells maintain IL- 12R.beta.2 expression when stimulated similarly. Here we show that the
loss of IL-12 responsiveness by BALB/c T cells involves the action of endogenous TGF- .beta.. BALB/c T cells stimulated in the presence of anti-TGF-.beta. specifically maintain IL-12 responsiveness, express IL-12R.beta.2 mRNA, and can stimulate nitric oxide production in peritoneal exudate cells. Low concentrations of TGF-.beta. added exogenously during primary activation of B10.D2 or F1 T cells significantly **inhibit** their development of IL-12 responsiveness. These effects of anti-TGF-.beta. are dependent on endogenous IFN-.gamma. and are **inhibited** by exogenously added IL-4. Thus, at least one effect of TGF-.beta. on Th1/Th2 development may be the attenuation of IL-12R.beta.2 expression.
CT Medical Descriptors:
*t lymphocyte activation
*immunoregulation
protein expression

antigen binding
peritoneum exudate
inhibition kinetics
binding affinity
concentration response
nonhuman
mouse
controlled study
animal tissue
animal cell
article
priority journal
Drug Descriptors:
*recombinant transforming growth factor beta: DO, drug dose
*recombinant transforming growth factor beta: PD, pharmacology
***interleukin 12: EC, endogenous compound**
*interleukin 12 receptor: EC, endogenous compound
messenger rna: EC, endogenous compound
nitric oxide: EC, endogenous compound
gamma interferon: EC, endogenous compound
recombinant interleukin 4: PD, pharmacology

L22 ANSWER 15 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998263227 EMBASE
TI Phagocytosis of Leishmania mexicana amastigotes by macrophages leads to a sustained suppression of IL-12 production.
AU Weinheber N.; Wolfram M.; Harbecke D.; Aebischer T.
CS T. Aebischer, Max-Planck-Institut fur Biologie, Abteilung Membranbiochemie, Correnssstrasse 38, D-72076 Tubingen, Germany. Toni.Aebischer@tuebingen.mpg.de
SO European Journal of Immunology, (1998) 28/8 (2467-2477).
Refs: 42
ISSN: 0014-2980 CODEN: EJIMAF
CY Germany
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Healing of leishmaniases is dependent on activation of parasitized macrophages (M.PHI.) by IFN-.gamma., which is secreted by Leishmania-specific Th1 cells. IL-12 enhances IFN-.gamma. production by Th1 cells and is crucial for cure. The host cells of Leishmania sp., M.PHI., are a main source of IL-12 in vivo. We report that infection of quiescent murine M.PHI. with L. mexicana or L. major amastigotes does not induce IL-12 production. Moreover, infection suppresses IL-12 secretion by M.PHI. activated by LPS, by CD40 cross-linking or cognate interaction with Th1 cells. IL-12 secretion is also suppressed in M.PHI. activated after phagocytosis of latex beads. Suppression is independent of engagement of CR3 or Fc.gamma.R during phagocytosis, is not mediated by IL-10 and does not alter steady state IL-12p40 mRNA levels. In addition, suppression of IL-12 secretion does not depend on M.PHI. activation concurrent to infection. In contrast, NO production was not **inhibited**. Thus, M.PHI. effector functions are differentially affected and this may be a general effect of phagocytosis of non-activating particles. The possible implications of this effect on the infection are discussed.

CT Medical Descriptors:
*amastigote
*phagocytosis
*macrophage
*leishmaniasis
cytokine production
leishmania mexicana
helper cell
host cell
nonhuman
female
mouse
animal experiment
animal model
controlled study
article
priority journal
Drug Descriptors:
***interleukin 12: EC, endogenous compound**
nitric oxide: EC, endogenous compound
cd40 antigen: EC, endogenous compound
messenger rna: EC, endogenous compound

L22 ANSWER 16 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998117320 EMBASE
TI Mice lacking inducible nitric-oxide synthase are more susceptible to herpes simplex virus infection despite enhanced Th1 cell responses.
AU MacLean A.; Wei X.-Q.; Huang F.-P.; Al-Alem U.A.H.; Chan W.L.; Liew F.Y.
CS F.Y. Liew, Department of Immunology, University of Glasgow, Glasgow G11 6NT, United Kingdom. f.y.liew@clinmed.gla.ac.uk
SO Journal of General Virology, (1998) 79/4 (825-830).
Refs: 29
ISSN: 0022-1317 CODEN: JGVIAY
CY United Kingdom
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB Mice deficient in the inducible nitric-oxide synthase (iNOS), constructed by gene-targeting, were significantly more susceptible to herpes simplex virus (HSV)-1 infection, displayed a delayed clearance of virus from the dorsal root ganglia (DRG) and exhibited an increase in the frequency of virus reactivation in DRG compared with similarly infected heterozygous mice. The infected iNOS-deficient mice developed enhanced Th1-type immune responses and their spleen cells produced higher concentrations of IL-12 than similarly infected heterozygous mice. This finding suggests that iNOS
plays an important role in resistance against HSV-1 infection. Furthermore, nitric oxide (NO) may block the development of Th1 cells via **inhibition** of IL-12 synthesis and thereby play a role in immune regulation.
CT Medical Descriptors:
*helper cell
*herpes simplex virus
gene targeting

spinal ganglion
spleen cell
cytokine production
enzyme deficiency
infection sensitivity
nonhuman
mouse
animal experiment
controlled study
animal cell
article
priority journal
Drug Descriptors:
***nitric oxide synthase: EC, endogenous compound**
***interleukin 12: EC, endogenous compound**

L22 ANSWER 17 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 1998071858 EMBASE
TI Suppression of IL-12 production by phosphodiesterase **inhibition** in murine endotoxemia is IL-10 independent.
AU Hasko G.; Szabo C.; Nemeth Z.H.; Salzman A.L.; Sylvester Vizi E.
CS E. Sylvester Vizi, Department of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, POB 67, H-1450 Budapest, Hungary.
ESVIZI@KOKI.HU
SO European Journal of Immunology, (1998) 28/2 (468-472).
Refs: 15
ISSN: 0014-2980 CODEN: EJIMAF
CY Germany
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Phosphodiesterase (PDE) **inhibitors** are potent regulators of various immune processes. Immune cells contain type IV and type III PDE. Here we studied in mice the effects of rolipram, a selective PDE IV **inhibitor**, and amrinone, a selective PDE III blocker, on plasma levels of IL-12 (p70), IFN-.gamma., IL-1, TNF-.alpha., and nitric oxide (NO) induced by intraperitoneal injection of Escherichia coli lipopolysaccharide (LPS) (80 mg/kg). Pretreatment of BALB/c mice with both rolipram (1-25 mg/kg) and amrinone (10-100 mg/kg) decreased plasma IL-12 levels in a dose-dependent manner. Similarly, LPS-elicited plasma IFN-.gamma. concentrations were suppressed by both rolipram and amrinone. However, LPS-induced plasma IL-1.alpha. levels were not affected by either of these compounds. In addition, rolipram **inhibited** IL-12, IFN-.gamma., TNF-.alpha. and nitrite/nitrate (breakdown products of NO) production in C57BL/6 IL-10(+/+) mice as well as in their IL-10-deficient counterparts (C57BL/6 IL-10(-/-)). Our results suggest that rolipram and amrinone decrease the immune activation in endotoxemia through **inhibition** of the production of pro-inflammatory mediators IL-12, IFN-.gamma., TNF-.alpha. and NO. These effects are not the consequences of the increase in IL-10 production by PDE **inhibition**.

CT Medical Descriptors:
*endotoxemia
nonhuman
male
mouse
animal experiment
article
priority journal
Drug Descriptors:
***interleukin 12: EC, endogenous compound**
*interleukin 10: EC, endogenous compound
*rolipram
*amrinone
phosphodiesterase inhibitor
gamma interferon: EC, endogenous compound
interleukin 1: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound
nitric oxide: EC, endogenous compound
escherichia coli lipopolysaccharide

L22 ANSWER 18 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97245846 EMBASE
DN 1997245846
TI Lipopolysaccharide and monophosphoryl lipid A differentially regulate interleukin-12, gamma interferon, and interleukin-10 mRNA production in murine macrophages.
AU Salkowski C.A.; Detore G.R.; Vogel S.N.
CS S.N. Vogel, Microbiology/Immunology Department, USUHS, 4301 Jones Bridge Rd., Bethesda, MD 20814, United States. vogel@usuhsb.usuhs.mil
SO Infection and Immunity, (1997) 65/8 (3239-3247).
Refs: 67
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Monophosphoryl lipid A (MPL) is a nontoxic derivative of the lipid A region of lipopolysaccharide (LPS) that is being developed as both an adjuvant and prophylactic drug for septic shock. We compared the ability of LPS and MPL to induce interleukin-10 (IL-10), IL-12 p35, IL-12 p40, gamma interferon (IFN-.gamma.), glucocorticoid receptor (GR), IL-1 receptor **antagonist** (IL-1ra), and inducible nitric oxide synthase mRNA expression in murine peritoneal macrophages. These genes were chosen for their ability to positively or negatively regulate the host immune response and thus for their potential involvement in MPL-induced adjuvanticity or in its ability to protect against sepsis. LPS was a more potent inducer of IL-12 p35, IL-12 p40, and IFN-.gamma. mRNA, as well as of IL-12 protein, than MPL. In contrast, MPL induced higher levels of IL-10 mRNA than did LPS from 1 to 1,000 ng/ml. In general, MPL was not a more potent inducer of negative regulatory genes, since MPL and LPS induced similar levels of GR and IL-1ra mRNA. Addition of anti-IL-10 antibody to cultures increased the induction of MPL-induced IL-12 p35, IL-12 p40, and IFN-.gamma. mRNA, suggesting that the enhanced production of IL-10 by MPL-stimulated macrophages contributes to decreased production

of mRNA for IL-12 (p35 and p40) and IFN-.gamma.. Conversely, the addition of exogenous IL-10 to LPS-treated macrophages reduced the mRNA expression of these cytokine genes. These studies suggest that enhanced production of IL- 10 by MPL-stimulated macrophages may contribute to the reduced toxicity of MPL through its negative action on induction of cytokines shown to enhance endotoxicity.

CT Medical Descriptors:
*peritoneum macrophage
animal cell
article
cell stimulation
gene induction
mouse
nonhuman
priority journal
Drug Descriptors:
*escherichia coli lipopolysaccharide
*gamma interferon: EC, endogenous compound
*interleukin 10: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
*phosphoryl lipid a
cytokine antibody
glucocorticoid receptor: EC, endogenous compound
interleukin 1 receptor blocking agent: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound

L22 ANSWER 19 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97205418 EMBASE
DN 1997205418
TI Suppression of cyclophosphamide induced diabetes development and pancreatic Th1 reactivity in NOD mice treated with the interleukin (IL)-12 **antagonist** IL-12[p40)2.
AU Rothe H.; O'Hara R.M. Jr.; Martin S.; Kolb H.
CS Dr. H. Rothe, Diabetes Research Institute, Auf'm Hennekamp 65, D-40225 Dusseldorf, Germany
SO Diabetologia, (1997) 40/6 (641-646).
Refs: 38
ISSN: 0012-186X CODEN: DBTGAJ
CY Germany
DT Journal; Article
FS 003 Endocrinology
026 Immunology, Serology and Transplantation
LA English
SL English
AB The macrophage product interleukin (IL)-12 is known to drive Th1 reactions in physiological and pathological immune responses. Here we report that treatment with the homodimeric IL-12p40 subunit, an **antagonist** of the bioactive IL-12p35/p40 heterodimer, suppresses diabetes development in cyclophosphamide-injected NOD mice. Female mice of 70 days old received cyclophosphamide (250 mg/kg) to accelerate and synchronize diabetes development, and daily injections of 1 .mu.g IL-12(p40)2. While there was no delay of the first diabetes cases, the incidence of overt diabetes was

significantly decreased in treated mice (46 vs 23%, p < 0.05). Analysis of mRNA expression in the pancreas showed that administration of the IL-12 **antagonist** had dampened interferon-gamma gene expression, decreased the ratio of interferon-gamma/IL-10 mRNA levels and in parallel suppressed the expression of the inducible nitric oxide synthase. At the same time intra- islet infiltration was significantly decreased (p < 0.001). Interestingly, the administration of IL-12(p40)2 also affected IL-12 gene expression, by downregulation of p35 mRNA. We conclude that IL-12 p40 homodimer suppresses diabetes development in the NOD mouse by dampening islet inflammation via selective down-regulation of Th1 type responses. The naturally occurring IL- 12 **antagonist** IL-12(p40)2 represents a new and specific Th1 directed approach to prevent autoimmune diabetes.

CT Medical Descriptors:
*autoimmunity
*diabetes mellitus
*insulitis
animal experiment
animal tissue
article
immune response
macrophage
mouse
nonhuman
pathogenesis
priority journal
Drug Descriptors:
*cyclophosphamide
***interleukin 12**
gamma interferon
nitric oxide synthase

L22 ANSWER 20 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 97167915 EMBASE
DN 1997167915
TI Neospora caninum: Role for immune cytokines in host immunity.
AU Khan I.A.; Schwartzman J.D.; Fonseka S.; Kasper L.H.
CS I.A. Khan, Department of Medicine, Dartmouth Medical School, Hanover, NH 03755, United States
SO Experimental Parasitology, (1997) 85/1 (24-34).
Refs: 25
ISSN: 0014-4894 CODEN: EXPAAA
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Neospora caninum is a coccidial protozoan parasite that infects a large range of mammals including dogs, cats, mice, and cattle. Morphologically, N. caninum appears indistinguishable from Toxoplasma gondii, although they are genetically distinct. To date there have been no reported cases of this infection in humans, although nonhuman primates may be susceptible to infection. Inbred A/J mice develop no clinical and little histologic

evidence of infection in spite of a high-dose inoculum of N. caninum. Splenocytes obtained from infected mice proliferate in vitro in response to both N. caninum and T. gondii-soluble antigen. A transient state of T cell hyporesponsiveness to parasite antigen and mitogen was observed at Day 7 p.i. This downregulatory response could be partially reversed by the addition of the nitric oxide **antagonist** LNMMA, but not antibody to IL-10. Mice infected with N. caninum produce significant quantities of IL-12 and IFN.gamma., most evident shortly after infection. In vivo, antibody to IF-12 is able to neutralize immune resistance to the parasite. Moreover, in vivo depletion of IFN.gamma. with antibody renders the mice susceptible to infection. These observations suggest that N. caninum induces a T cell immune response in the infected host that is at least partially mediated by IL-12 and IFN.gamma..

CT Medical Descriptors:
*host parasite interaction
*neospora caninum
animal experiment
apicomplexa
article
controlled study
female
histology
immunity
immunosuppressive treatment
mouse
nonhuman
priority journal
Drug Descriptors:
*interleukin 10: EC, endogenous compound
***interleukin 12: EC, endogenous compound**
***nitric oxide: EC, endogenous compound**

L22 ANSWER 21 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96325754 EMBASE
DN 1996325754
TI Regulation of microglial activation by TGF-.beta., IL-10, and CSF-1.
AU Lodge P.A.; Sriram S.
CS Multiple Sclerosis Res. Laboratory, Vanderbilt Stallworth Rehabilit Hosp, 2201 Capers Ave,Nashville, TN 37212, United States
SO Journal of Leukocyte Biology, (1996) 60/4 (502-508).
ISSN: 0741-5400 CODEN: JLBIE7
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Microglia are the resident macrophages of the brain and as such are active participants in immune responses in the central nervous system. Normal resting microglia express low levels of MHC class I and class II antigens and do not produce proinflammatory cytokines. However, microglial immune functions are induced in areas of infection or injury, To understand regulation of cytokines that are secreted by and act upon microglia, we

examined production of interleukin (IL)-12, tumor necrosis factor-a (TNF-.alpha.), and nitric oxide (NO) by lipopolysaccharide (LPS)-stimulated microglia. We observed secretion of IL-12, TNF-.alpha., and NO following stimulation of microglia with LPS. Addition of IL-10 suppressed TNF-.alpha., IL-12, and NO production, Transforming growth factor-.beta. (TGF-.beta.) also **inhibited** TNF-.alpha. and NO but did not affect IL-12 secretion, IL-12 secretion became sensitive to TGF-.beta. **inhibition** when microglia were cultured in the absence of CSF-1. In addition to its effect on the response to TGF-.beta. CSF-1 suppressed the response of microglia to LPS. These data suggest that CSF-1 may contribute to the immunologically privileged status of the central nervous system.

CT Medical Descriptors:
*macrophage activation
*microglia
article
controlled study
mouse
nonhuman
priority journal
Drug Descriptors:
*colony stimulating factor: PD, pharmacology
*interleukin 10: PD, pharmacology
***interleukin 12: EC, endogenous compound**
***nitric oxide: EC, endogenous compound**
*transforming growth factor beta: PD, pharmacology
*tumor necrosis factor alpha: EC, endogenous compound
lipopolysaccharide

L22 ANSWER 22 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96257660 EMBASE
DN 1996257660
TI Interferon-.gamma. induced type I nitric oxide synthase activity **inhibits** viral replication in neurons.
AU Komatsu T.; Bi Z.; Reiss C.S.
CS Department of Biology, New York University,New York, NY 10003, United States
SO Journal of Neuroimmunology, (1996) 68/1-2 (101-108).
ISSN: 0165-5728 CODEN: JNRIDW
CY Netherlands
DT Journal; Article
FS 004 Microbiology
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Type I NOS expression increases in OB neurons during VSV infection. Immunocytochemical Staining of NB41A3 cells indicates constitutive expression of interferon (IFN)-.gamma. receptor and type I NOS. IFN-.gamma. treatment of NB41A3 cells increased NO production and type 1 NOS protein. In vitro replication of VSV, polio virus type 1, and Herpes Simplex virus type 1 (HSV-1) is significantly **inhibited** by IFN-.gamma. induced type I NOS and antagonized by NOS **inhibitors**. In contrast, while IFN-.gamma. treatment **inhibited** influenza and Sindbis virus replication, a different pathway(s) was involved. The

isoform-selective NOS **inhibitor**, 7-nitroindazole (7NI) was used to treat mice, resulting in a 10-fold higher titer of virus in brain homogenates, and abrogated the recovery-promoting effect of interleukin-12 treatment. Thus, IFN-.gamma. induced type I NOS activity may play an important role in host immunity against neurotropic viral infections.

CT Medical Descriptors:
*nerve cell
*vesicular stomatitis virus
*virus infection: ET, etiology
*virus infection: DT, drug therapy
***virus inhibition**
animal experiment
article
controlled study
immunocytochemistry
mouse
nonhuman
priority journal
virus replication
Drug Descriptors:
*7 nitroindazole: PD, pharmacology
*gamma interferon: PD, pharmacology
*indazole: PD, pharmacology
***interleukin 12: PD, pharmacology**
***nitric oxide: EC, endogenous compound**
***nitric oxide synthase: EC, endogenous compound**
recombinant gamma interferon: PD, pharmacology
recombinant interleukin 12: PD, pharmacology
unclassified drug

L22 ANSWER 23 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96137575 EMBASE
DN 1996137575
TI The role of interleukin 12 and nitric oxide in the development of spontaneous autoimmune disease in MRL/MP-lpr/lpr mice.
AU Huang F.-P.; Feng G.-J.; Lindop G.; Stott D.I.; Liew F.Y.
CS Department of Immunology, Western Infirmary, University of Glasgow,Glasgow G11 6NT, United Kingdom
SO Journal of Experimental Medicine, (1996) 183/4 (1447-1459). ISSN: 0022-1007 CODEN: JEMEAV
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB MRL/MP-lpr/lpr (MRL/lpr) mice develop a spontaneous autoimmune disease. Serum from these mice contained significantly higher concentrations of nitrite/nitrate than serum from age-matched control MRL/MP-+/+ (MRL/+), BALB/c or CBA/6J mice. Spleen and peritoneal cells from MRL/lpr mice also produced significantly more nitric oxide (NO) than those from the control mice when cultured with interferon (IFN) .gamma. and lipopolysaccharide (LPS) in vitro. It is interesting to note that peritoneal cells from MRL/lpr mice also produced markedly higher concentrations of interleukin (IL) 12 than those from MRL/+ or BALB/c mice when cultured with the same stimuli. It is striking that cells from MRL/lpr mice produced high

concentrations of NO witch cultured with IL-12 and IPS, whereas only low or background levels of NO were produced by similarly cultured cells from MRL/+ or BALB/c mice. The enhanced NO synthesis induced by IFN-.gamma./LPS was substantially **inhibited** by anti-IL-12 antibody. In addition, IL-12-induced NO production can also be markedly **inhibited** by anti-IFN-.gamma. antibody, but only weakly **inhibited** by anti-tumor necrosis factor .alpha. antibody. The effect of IL-12 on NO production was dependent on the presence of natural killer and possibly T cells. Serum from MRL/lpr mice contained significantly higher concentrations of IL-12 compared with those of MRL/+ or BALB/c control mice. Daily injection of recombinant IL-12 led to increased serum levels of IFN-.gamma. and NO metabolites, and accelerated glomerulonephritis in the young MRL/lpr mice (but not in the MRL/+ mice) compared with controls injected with phosphate-buffered saline alone. These data, together with previous finding that NO synthase **inhibitors** can ameliorate autoimmune disease in MRL/lpr mice, suggest that the high capacity of such mice to produce IL-12 and their greater responsiveness to IL-12, leading to the production of high concentrations of NO, are important factors in this spontaneous model of autoimmune disease.

CT Medical Descriptors:
*autoimmunity
animal cell
animal model
article
controlled study
glomerulonephritis: ET, etiology
immunopathogenesis
male
mouse
nonhuman
peritoneum cell
priority journal
spleen cell
etiology
Drug Descriptors:
***interleukin 12**
***nitric oxide**
gamma interferon
lipopolysaccharide

L22 ANSWER 24 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96100252 EMBASE
DN 1996100252
TI Interleukin-12 and tumor necrosis factor alpha mediate innate production of gamma interferon by group B streptococcus-treated splenocytes of severe combined immunodeficiency mice.
AU Derrico C.A.; Goodrum K.J.
CS Department of Biological Sciences, Irvine Hall, Ohio University,Athens, OH 45701-2979, United States
SO Infection and Immunity, (1996) 64/4 (1314-1320).
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article

FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB The existence of interleukin-12-mediated innate immune responses to group B streptococci (GBS) was tested by examining T-lymphocyte-independent gamma interferon (IFN) production in cultured splenocytes from severe combined immunodeficiency mice. Splenocytes were cultured with killed or living GBS for 48 h, and then IFN was measured by enzyme-linked immunosorbent assay. Type III GBS as well as other extracellular bacterial agents of neonatal sepsis (staphylococci and enterococci) induced IFN production, which was enhanced by interleukin-2 and was **inhibited** by neutralizing antibodies to tumor necrosis factor alpha and to mouse interleukin-12. Interleukin-12 bioactivity was present in conditioned medium from GBS-treated adherent macrophages. Adherent peritoneal macrophages and bone marrow-derived natural killer cells from severe combined immunodeficiency mice cultured separately with GBS did not produce IFN, whereas cocultures did produce IFN. Functional macrophage activation was evident by nitric oxide production in GBS-treated splenocyte cultures. The results show that extracellular pathogens such as GBS, similarly to intracellular microbes, induce macrophage interleukin-12 and tumor necrosis factor alpha, which promote natural killer cell secretion of IFN, which then enhances innate phagocyte resistance mechanisms.
CT Medical Descriptors:
*combined immunodeficiency
*spleen cell
*streptococcus agalactiae
animal cell
animal model
article
colorimetry
enzyme linked immunosorbent assay
human
human cell
immune response
macrophage activation
mouse
natural killer cell
nonhuman
phagocyte
priority journal
t lymphocyte
Drug Descriptors:
*gamma interferon: EC, endogenous compound
interleukin 12: EC, endogenous compound
*tumor necrosis factor alpha: EC, endogenous compound
interleukin 2
neutralizing antibody
nitric oxide: EC, endogenous compound

L22 ANSWER 25 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 96094931 EMBASE
DN 1996094931

TI Bacterial superantigen-induced human lymphocyte responses are nitric oxide
dependent and mediated by IL-12 and IFN-.gamma..
AU Sriskandan S.; Evans T.J.; Cohen J.
CS Infect. Diseases/Bacteriology Dept., Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road,London W12 ONN, United Kingdom
SO Journal of Immunology, (1996) 156/7 (2430-2435).
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Bacterial superantigens cause marked proliferation of T cells and release of lymphokines. Nitric oxide, derived from the conversion of L-arginine to
L- citrulline, **inhibits** this activation in murine cells. We have now investigated the roles of IL-12, IFN-.gamma., lymphotoxin-.alpha., and
nitric oxide during superantigen-induced human lymphocyte activation. Lymphocyte activation was determined by measurement of proliferative responses and lymphokine release. Both toxic shock syndrome toxin-1 from Staphylococcus aureus and recombinant streptococcal pyrogenic exotoxin A induced proliferation and production of IFN-.gamma., lymphotoxin-.alpha., and IL-12 by human mononuclear cells in a time-dependent fashion. The release of IFN-.gamma. was abrogated by a neutralizing Ab to IL-12, but lymphocyte proliferative responses were unaffected. A neutralizing Ab to IFN-.gamma. prevented the release of lymphotoxin-.alpha., but did not affect proliferation. The neutralization of lymphotoxin-.alpha. using two different Abs did not affect IFN-.gamma. release or proliferation. In contrast to previous findings in mice, the arginine analogue, N(G)-monomethyl-L-arginine, significantly **inhibited** both proliferation and lymphokine release by superantigen-stimulated human cells. Thus, the release of lymphotoxin-.alpha. by lymphocytes following superantigen stimulation is dependent upon the presence of IFN-.gamma.; the IFN-.gamma. response is in turn under the control of IL-12. There is no evidence that nitric oxide plays an **inhibitory** role during superantigen-mediated human lymphocyte activation. Indeed, arginine is a prerequisite for such activation.
CT Medical Descriptors:
*septic shock
*superinfection
*t lymphocyte
article
cell proliferation
human
human cell
lymphocyte activation
priority journal
staphylococcus aureus
Drug Descriptors:
*gamma interferon
***interleukin 12**
***nitric oxide**
*superantigen

L22 ANSWER 26 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 96062974 EMBASE
DN 1996062974
TI Leishmania promastigotes selectively **inhibit** interleukin 12 induction in bone marrow-derived macrophages from susceptible and resistant mice.
AU Carrera L.; Gazzinelli R.T.; Badolato R.; Hieny S.; Muller W.; Kuhn R.; Sacks D.L.
CS Laboratory of Parasitic Diseases, NIAID, NIH,Bethesda, MD 20892, United States
SO Journal of Experimental Medicine, (1996) 183/2 (515-526).
ISSN: 0022-1007 CODEN: JEMEAV
CY United States
DT Journal; Article
FS 004 Microbiology
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LA English
SL English
AB Leishmania major promastigotes were found to avoid activation of mouse bone marrow-derived macrophages (BMMo) in vitro for production of cytokines that are typically induced during infection with other intracellular pathogens. Coexposure of BMMo to the parasite and other microbial stimuli resulted in complete **inhibition** of interleukin (IL) 12 (p40) mRNA induction and IL-12 release. In contrast, mRNA and protein levels for IL-1.alpha., IL-1.beta., tumor necrosis factor (TNF) .alpha., and inducible NO synthase (iNOS) were only partially reduced, and signals for IL-10 and monocyte chemoattractant protein (MCP-1/JE) were enhanced. The parasite could provide a detectable trigger for TNF-.alpha. and iNOS in BMMo primed with interferon (IFN) .gamma., but still failed to induce IL-12. Thus IL-12 induction is selectively impaired after infection, whereas activation pathways for other monokine responses remain relatively intact. Selective and complete **inhibition** of IL-12 (p40) induction was observed using BMMo from either genetically susceptible or resistant mouse strains, as well as IL-10 knockout mice, and was obtained using promastigotes from cutaneous, visceral, and lipophosphoglycan- deficient strains of Leishmania. The impaired production of the major physiologic inducer of IFN-.gamma. is suggested to underlie the relatively prolonged interval of parasite intracellular survival and replication that is typically associate with leishmanial infections, including those producing self-limiting disease.
CT Medical Descriptors:
*leishmania major
*macrophage activation
animal cell
animal tissue
article
b lymphocyte
female
genetic susceptibility
immunoregulation
mouse
nonhuman
parasite survival

parasite virulence
priority journal
promastigote
strain difference
Drug Descriptors:
*gamma interferon
***interleukin 12: EC, endogenous compound**
interleukin 10
interleukin 1alpha
interleukin 1beta
messenger rna: EC, endogenous compound
monocyte chemotactic protein
nitric oxide synthase
tumor necrosis factor alpha

L22 ANSWER 27 OF 27 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 95208485 EMBASE
DN 1995208485
TI IL-12 prevents mortality in mice infected with Histoplasma capsulatum through induction of IFN-.gamma..
AU Zhou P.; Sieve M.C.; Bennett J.; Kwon-Chung K.J.; Tewari R.P.; Gazzinelli R.T.; Sher A.; Seder R.A.
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LA English
SL English
AB Histoplasma capsulatum is a pathogenic fungus found in discrete geographic locations throughout the world. The fungus invades the reticuloendothelial organs such as the spleen and liver of immunocompetent hosts where it is usually controlled. However, in individuals with immune deficiency, histoplasmosis is a severe and potentially fatal disease. Resistance to this infection is due primarily to a cellular immune response mediated by T cells and macrophages. Moreover, IFN-.gamma. is critical in activating macrophages to kill the organism. Herein we study the regulation of cytokine induction in mice infected with H. capsulatum and the effects of IL-12 in the course of infection. Mice infected with H. capsulatum and treated with neutralizing Abs to IFN-.gamma., TNF-.alpha., or IL-12 experienced accelerated mortality, indicating that endogenous production of these cytokines plays an important role in response to infection. In contrast, mice treated with IL-12 or a neutralizing Ab to IL-4 at the initiation of infection had substantially diminished mortality. Moreover, mice infected and treated with IL-12 show a two- to threefold increase in the amount of IFN-.gamma. following in vitro stimulation with specific H. capsulatum Ag compared with the control infected mice. The protective effect of IL-12 could be abrogated if a neutralizing Ab to IFN-.gamma. was given at the same time, demonstrating that the role of IL-12 in protection

was mediated by IFN-.gamma.. Additionally, infected mice treated with IL-12 had a severalfold decrease in the colony counts of H. capsulatum in spleen cells after 5 days of infection as compared with control animals. Lastly, spleen cells from infected animals treated with IL-12 showed a striking decrease in their proliferative response to mitogen or H. capsulatum Ag. Responses could be restored by adding **inhibitors** of IFN-.gamma. or of nitric oxide to the in vitro cultures. The above observations suggest that IL-12 may be useful in immunologic intervention against this opportunistic pathogen.

CT Medical Descriptors:
*histoplasma capsulatum
*histoplasmosis: DT, drug therapy
*mortality
animal cell
animal experiment
animal model
article
cell proliferation
controlled study
female
intraperitoneal drug administration
mouse
nonhuman
priority journal
spleen cell
survival
Drug Descriptors:
*aminoguanidine
*cytokine: EC, endogenous compound
*gamma interferon: EC, endogenous compound
interleukin 12: DT, drug therapy
interleukin 12: PD, pharmacology
*monoclonal antibody
*neutralizing antibody
concanavalin a
fungus antigen
interferon antibody
interleukin 4: EC, endogenous compound
messenger rna: EC, endogenous compound
nitric oxide: EC, endogenous compound
tumor necrosis factor alpha: EC, endogenous compound